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Measured Metabolic Requirement for Septic Shock Patients Before and After Liberation from Mechanical Ventilation

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Abstract

Objectives:

Negative energy balance can impair regeneration of the respiratory epithelium and limit the functionality of respiratory muscles, which can prolong mechanical ventilation. The present study sought to quantify and identify deviation in energy requirements of patients with septic shock during and upon liberation from mechanical ventilation.

Methods:

Patients admitted into intensive care with initial diagnosis of septic shock and mechanical ventilation-dependent were recruited. Their metabolic requirements before and after liberation from mechanical ventilation were measured by indirect calorimetry. Paired t-test was used to examine the variance between the two modes of breathing and Spearman rho correlation coefficient to examine relationship of selected indicators.

Results:

Thirty-five patients, 20 males and 15 females mean age 69 ±10 years, body height of 1.58 ±0.08 meters, and ideal body weight 59.01 ±7.63 kg were recruited. Median APACHEII score was 22, length of stay in the intensive care was 45 ±65 days and duration on mechanical ventilation was 24 ±25 days. Measured energy expenditure during ventilation was 2090 ±489 $kcal \cdot d^{-1}$ upon liberation from ventilation was 1910 ±579 $kcal \cdot d^{-1}$, and actual caloric intake was 1148 ±495 $kcal \cdot d^{-1}$. Paired-t test showed that measured energy expenditure ($p=0.02$), actual calories provision and energy expenditure with ($p=0.00$) and without ($p=0.00$) ventilator support were all significantly different. Mean carbohydrate oxidation was 0.17 ±0.09 $g \cdot min^{-1}$ when patients were on mechanical ventilation compared to 0.14 ±0.08 $g \cdot min^{-1}$ upon liberalization from it, however, the results were not statistically significant.

Furthermore, mean lipid oxidation was 0.08 ±0.05 $g \cdot min^{-1}$ during mechanical ventilation and 0.09±0.07 $g \cdot min^{-1}$ upon liberalization from it and the mean difference was not statistically significant.

Spearman correlation coefficient showed a positive relationship between actual calorie provision and duration of stay in intensive care (r=0.41 and p=0.01) and duration on mechanical ventilation (r=0.55 and p=0.00). Oxygen consumption (r=0.49 and p=0.00) and carbon dioxide production (r=0.4 and p=0.02) were moderately strong and positive during and upon liberation from mechanical ventilation. Correlation between lipid oxidation and oxygen consumption during ventilation (r=0.74, p=0.00) and after ventilation (r=0.82, p=0.00) as well as lipid oxidation and carbon dioxide production during ventilation (r=0.37, p=0.03) and liberation from ventilator (r=0.91, p=0.00) were significantly correlated with each other in grams per minute only.

Conclusions:

This is a pioneering study to examine energy expenditure and substrate utilization and oxidation within a single cohort of patients. The lower measured energy expenditure upon liberation from mechanical ventilation among critically ill patients could result from positive pressure support from ventilation, the repeated cycle of “rest” and “work” during weaning from ventilators and the asynchronization between self-initiated breathing effort and the ventilatory support. The positive relationship in duration on mechanical ventilation and length of stay with calorie consumption could be longer stay led to more time for progression to reach nutrition targets. . Any discrepancy in energy expenditure and substrate utilization with and without ventilatory support should be monitored. Future studies are important to examine whether matching energy expenditure with energy intake could promote positive clinical outcomes.

Contents

Glossary of Terminologies

Acute phase protein – proteins that are secreted from the liver in increasing or decreasing amount in the blood as a result of trauma, inflammation, or disease. These proteins can inhibit or mediate inflammatory processes

Anabolism – the synthesis of complex molecules in living organisms from simpler ones together with the storage of energy; constructive metabolism

Atrophy – loss in net protein content and fat-free mass due to an imbalance between protein synthesis and protein degradation.

Catabolism – the breakdown of complex molecules in living organisms to form simpler ones, together with the release of energy; destructive metabolism

Critically ill – patients who are experiencing an acute life-threatening episode or who is believed to be in imminent danger of such an episode

Energy expenditure – energy that is required to sustain bodily functions in the waking state and work including exercise

Indirect calorimetry – measurement of a person's oxygen uptake at rest and under conditions of steady-rate exercise

Malnutrition – lack of proper nutrition, caused by not having enough to eat, not eating enough of the right things, or being unable to use the food that one does eat.

Mechanical ventilation – In medicine, mechanical ventilation is a method to

mechanically assist or replace spontaneous breathing.

Nutrition support –provision of nutrients and any necessary adjunctive therapeutic agents to patients orally and/or enterally by administration into the stomach or intestine and/or by intravenous infusion (parenterally) for the purpose of improving or maintaining a patient's nutrition status'

Oxidation – process of a substance combining with oxygen

Respiratory exchange ratio – interchange with respiratory quotient (RQ) and strongly influenced by ventilation and pulmonary blood flow

Respiratory quotient – carbon dioxide production by the body divided by the oxygen consumption during metabolism of dietary intake

Sepsis – the presence in tissues of harmful bacteria and their toxins, typically through infection of a wound.

Septic shock – when fever, chills, tachycardia, tachypnea, and altered mental function, the signs of acute septicemia, are combined with hypotension and signs of inadequate organ perfusion

Substrates – an underlying substance or layer.

$\dot{V}_{O2}$ – symbol for oxygen consumption per unit of time

$\dot{V}_{CO2}$ – symbol for carbon dioxide output per unit of time

Weaning – to detach from a source of dependence

Chapter 1: Literature Search and Definitions

Database used for literature review included All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED, Ovid MEDLINE(R) without Revisions 1996 to November Week 2 2012 and JOURNALS@OVID FULL TEXT. There is scarce research on indirect calorimetry measurement and expenditure of septic patients with and without mechanical ventilation, thus, search strategy and keywords became more general in order to include all possible literature relevant to the topic.

1. Review of metabolism and energy

The study begins with introduction to metabolism and its relationship to energy intake and expenditure. Keywords including metabolism, metabolic assessment, hypermetabolism, hypometabolism, energy expenditure, energy requirement, and combination of the above are used.

2. Review of components contributing to human metabolism

Human metabolism is used to search relevant parameters that relates and influences energy expenditure or metabolism. General description of anthropometric, specific indicators including body height, body weight, body composition and metabolically active tissues are used as well. Physical stress has been added to identify literatures about external impact on energy expenditure of individual.

3. Overview of various methodologies to measure human metabolism

A comprehensive literature review has been performed to include in the discussion of methodologies for assessing human metabolism. Keywords “metabolism” and “measurement” are used to identify relevant articles to provide general overview of different metabolic assessment methods.

4. Review use of predictive equations to assess energy expenditure of the ill population

The use of predictive energy expenditure is common for estimating energy expenditure among patient population. Predicted equations and energy expenditure are used to identify target literatures about comparison and application of predicted equation to estimate energy expenditure for patients with various clinical conditions.

5. Review of indirect calorimetry

Indirect calorimetry is a unique device for measuring real-time individual energy expenditure. It is often being used to develop predicted equations in specific patient populations as well as direct clinical application in hospital setting to meet energy requirement for different patient groups. Indirect calorimetry is often used as a practical "standard" for developing many well-established predicted equations for estimating energy expenditure. Nonetheless, the combination keywords search of indirect calorimetry and "weaning" do not yield any relevant study. Indirect calorimetry itself has yielded hundreds of literatures. It is then narrowed down by combining keywords including very ill, intensive care, sepsis, hospital and clinical setting. Various types of calorimeter are also described in this paper and include detail account of patient preparation and application of data after measurement. Furthermore, interpretation and application of indirect calorimetry have been extensively discussed throughout the paper.

6. Review of energy balance and clinical outcomes

Nutrition and clinical outcomes are keywords for searching literatures in relation to clinical outcomes. Therefore, critically ill and energy deficit and length of hospital were combined to locate articles on relationship

between hospital outcomes and energy balance.

7. Review of definition of sepsis and septic shock

A clear definition of sepsis and septic shock are essential to proper patient recruitment in this study. Sepsis and septic shock word search has yielded many highly relevant references which promotes proper definition of patient recruitment criteria.

8. Review of metabolic requirement and respiration

An overview of energy requirement, work of breathing and respiration were identified through keyword search respiration and metabolism, mechanical ventilation and energy expenditure, weaning and mechanical ventilation and to further filter the search through combining with critically ill or intensive care. An additional protocol was included to accommodate indirect calorimetry measurement on mechanical ventilator-dependent patients using endotracheal-tube (ETT). Literatures on automatic tracheal compensation (ATC) in combination with the above keywords were used to search for available evidence.

9. Review of Mechanical Ventilation and Weaning

Metabolic requirement and energy utilization were used separately and in combination with weaning or mechanical ventilation, energy expenditure and intensive care to locate articles of interest.

10. Review of Clinical Outcome and Application of Indirect Calorimetry

Keywords search using combination of clinical outcomes, nutrition, nutrition support, enteral nutrition support with application and indirect calorimetry. There was no specific article directly addressing the above areas but numerous literatures with themes in nutrition support and positive

clinical outcomes were located.

Chapter 2: Overview of Metabolic Components and Assessment

Origin and Significance of Metabolism

Energy requirement is an estimate of energy consumption taking into account body mass, level of physical activity as well as growth, pregnancy, lactation, maintenance and recovery. Daily energy is produced by food digestion, absorption and metabolism. The source of energy in the human body originates from nutrients, specifically macronutrients including carbohydrates, proteins, fats and a small portion from alcohol. The digestive and absorptive processes break the chemical bonds within food and allow it to be utilized and metabolized by the body for generation of energy. Energy is crucial for our survival and bodily functions. Total energy expenditure varies among individuals because of different physical activity, stressors, etc. (Frary and Johnson, 2000). It is important to understand different components that can vary individual metabolic requirement.

Total Energy Expenditure

Total energy expenditure is the amount of energy (calories) that an individual uses to breathe, circulate blood, digest food, and be physically active. Total energy expenditure includes about 60-70% of resting energy expenditure, 8-10% thermic effect from food and remaining from physical activity and growth. Energy is also required to tackle severity and duration of diseases and subsequent healing processes (Brandi et al, 1999). Energy or caloric intake should be in balance with energy expenditure to minimize weight change (Walker and Heuberger, 2009).

Basal Metabolic Rate

According to Walker and Heuberger (2009), resting metabolic rate was the minimum energy for maintaining vital bodily functions when the individual was awake. Resting metabolic rate measures the minimum metabolic

activity after waking prior to getting out of bed. Basal energy expenditure is heat production from the body and can be measured indirectly by obtaining information on oxygen uptake under controlled conditions. Basal metabolic rate is the expression of metabolic activity from body mass. It is the lowest level of energy expenditure when an individual is at rest and a comparatively small proportion in the total energy expenditure (Ainslie, Reilly, and Westerterp, 2003).

Resting Energy Expenditure

Resting energy expenditure is often interchangeable with basal energy metabolic rate and refers to energy for normal cellular maintenance, organ function and body temperature. It is around 75 to 100% of total energy expenditure in the critically ill. In the healthy population, 60 to 70% of resting energy may be used to maintain cellular functions, basic metabolic processes and muscular functions (Walker et al, 2009). Basal metabolic rate being measured in strict controlled research environment will only be slightly lower than the resting energy expenditure. Resting energy expenditure is usually measured after 3 to 4 hours fast and without prior physical activity (McArdle, Katch and Katch, 1991). Since it is not always practical to measure basal metabolic rate, resting energy expenditure becomes the closest indicator for energy expenditure when body was at rest. Theoretically resting energy expenditure is higher than basal metabolic rate.

Jacobs and Wong (2000) stated that it was difficult to obtain true basal state on patients in intensive care setting and thus, measurement of resting energy expenditure was more commonly applied in patients. Resting energy expenditure is the energy used by patients to perform activities of daily living and minimal physical activity. The increase in energy

expenditure can be in proportion to the patients' physiologic stress for instance, fever elevates resting energy expenditure for every degree Celsius increases in core temperature.

Factors Impact on Total Energy Expenditure

Ageing, Surface Area and Body Composition

McArdle et al (1996) stated that estimation of resting metabolic rate could be accomplished by multiplying basal metabolic rate by the surface area computed from stature and mass, mainly fat free mass because of its metabolically active nature. Body surface area was only a good index of resting metabolism in reference to lean body mass for an individual or group of individuals of the same gender. There is strong association between body surface area and lean body mass within a particular gender. Females often possesses smaller lean body mass than males and thus, a difference in resting metabolic rate does not necessarily imply lower surface area for the specific gender. The lower basal metabolic rate in women than men can relate to higher body fat in females than males of similar body size (Frary and Johnson, 2000). Chambers, Moylan and Reid (2009) reviewed that fat free mass or lean muscle mass atrophied among the critically ill population through studying muscles unloading mechanism. Unloading mechanism is due to force per unit mass is significantly diminished in unloaded (atrophied) muscles. Stress-induced muscle wastage, lack of timely physical rehabilitation and inadequate nutrition support can reduce muscle mass preservation. Moylan and Reid (2009) mentioned that critically ill patients with marked muscle wasting could possess lower energy metabolism.

Climate

Lichtenbelt, Schrauwen, Kerckhove, and Westerterp-Plantenga (2002)

studied energy expenditure and change in body temperature among 9 males. Subjects were placed individually in a respiration chamber that was set at 22 and 16 degree Celsius in random order. Lichtenbelt et al (2002) found that there was significant inter-individual variation in both rectal and skin temperature measurements and energy expenditures after adjustment of body composition. Authors concluded that short-term exposure to low environmental temperature led to significant decrease in skin and core body temperatures but subsequent increased in energy expenditure was also observed. The change in body temperature gradient was negatively related to energy expenditure (R^2=0.82 and $p<0.002$). The study demonstrated that low core temperature was induced by the environment led but resulted in elevation of energy expenditure.

Thermic Effect of Food (TEF)

Thermic effect of food is the energy required during food digestion, assimilation, and/or storage which also counts towards part of total energy expenditure. Thermic effect of food is also equivalent to postprandial thermogenesis meaning an increase in heat production after ingestion of a meal. Postprandial thermogenesis lasts for hours and can vary with composition of diets. Thermic effect of food was difficult to quantify in the very ill and extreme body mass because of variation in food consumption, types and delivery methods of feeding regimens (Frary and Johnson, 2000).

Segal, Edaňo, Blando and Pi-Sunyer (1990) found that thermic effect of food among obese individuals while they were overfed could be blunted. An additional absolute (720 kilocalories) and relative caloric load (35% individual resting energy expenditure) were provided to 2 groups of individuals, the obese and lean. A 3-hour postprandial thermic effect of

food was found to be higher in the lean than obese group in both absolute (69 ±4 vs. 31 ±3 kilocalories per 3-hour and $p<0.01$) and relative caloric loads (64 ±4 vs 37 ±3 kilocalories per 3-hour and $p<0.01$). Authors concluded that there could be defect in the thermic effect of food among the obese

Growth

Growth requires energy for tissue synthesis and deposition in new tissues for storage and can vary with the amount and types of tissues. It is very difficult to define and measure precise energy cost for growth or tissue synthesis in the young population because it is a gradual process that takes time to become measurable. Sick infants and young children in recovery may require additional energy for catch-up growth and recovery simultaneously. Butte (2004) reviewed energy estimation and deposition of infants during growth. Energy deposition decreased between 1 to 12 months of age and energy utilization was mainly for tissue synthesis. Brooke, Alvear and Arnold (1979) studied energy balance among 15 infants between Day 10 to 29. These infants were fed standard infant formulary and their growth and energy balance were measured. Results showed that the mean gross energy intake of the cohort was 181 kilocalories and 79% was retained. The mean resting metabolic rate increased as the cohort matured. The energy cost of weight gain was 5.6 kilocalories per gram and energy stored in new tissue was 4.0 kilocalories per gram.

Factors Impacting on Individual Total Energy Expenditure

Physical Activity

Physical activity can be one of the most variable components in calculating total energy expenditure. Most healthy individuals can sustain metabolic rate that is 10 times the resting values especially with large muscle exercises, such as brisk walking, running and swimming. Energy

expenditure for physical activities can vary among healthy individuals and contribute to different proportion in total energy expenditure (McArdle, Katch and Katch, 1991). Furthermore, physical activities can slow down loss of fat free mass (muscles) and maintain comparatively higher resting energy expenditure than those who sustained a sedentary lifestyle. The same applies to resting metabolic rate during aging process with higher lean body mass and resting metabolic rate (Frary and Johnson, 2000).

Strath et al (2013) classified physical activity into structured or incidental. Structured physical activity or exercise was intentionally planned activity for obtaining the benefits of health and fitness. The incidental physical activity was spontaneous and often referring to daily activities at work, at home or during transport. Authors mentioned that activities should be categorized into 4 dimensions that included mode or type of activity, frequency of performing activity, duration of performing activity and intensity of performing activity. The domains were referring to relation with occupation, domestic, transportation and leisure.

Metabolic equivalents (MET) are a tool to quantify energy expenditure for selected activities. METs are measuring units associate with individual metabolism during physical activity and vary according to exercise intensity. A MET value of 1 refers to utilization of oxygen at rest (3.5 ml of oxygen per kg of body weight per minute in adults) and can be expressed as 1 kcal per kg body weight per hour. Therefore, energy expenditure from physical activity can be estimated by multiplying body weight in kilograms by the METs and duration of the selected activity (Frary and Johnson, 2000).

Body Temperature

Besides physical activity, core body temperature has been shown to relate to change in energy expenditure. Matthews et al (1995) examined change in core temperature and whole body energy expenditure among 18 children with severe head injury receiving neuro-intensive care. Their mean rectal temperature was 37.8 degree Celsius. There was positive relationship within subjects between rectal temperature and energy expenditure. The energy expenditure of these children had increased by a mean of 7.4 kilocalories for every degree Celsius body temperature.

In summary, resting energy expenditure is only a part of total energy expenditure and thus, assessment is complex due to the variation in individual patient condition. Factors affecting total energy expenditure in patients or individuals with extreme body mass may be different than health population. The fluctuation in resting energy expenditure depending on severity of illness and treatment options and some of the factors affecting energy expenditure in healthy population may not apply.

Chapter 3: Introduction to Metabolic Condition of the Critically Ill

Resting Energy Expenditure of the Critically Ill

Knowledge of metabolic response and energy expenditure among the critically ill population remains complex, scarce and inconsistent. the information can facilitate clinicians to prescribe quality and appropriate nutrition support to meet patients' energy expenditure. Plank and Graham (2003) described metabolic response after acute traumatic injury as "ebb" and "flow" phase. *Ebb phase* usually lasts between 24 to 48 hours and patient will experience hypometabolic state. *Flow phase* occurs when patients have been stabilized but it is also a hypermetabolic condition with elevated energy demand and rapid tissue metabolism. Hypermetabolism increases oxygen consumption to promote substrate utilization and subsequent energy production for survival of vital organs. According to Fontaine and Muller (2011), hypermetabolic state in the very ill population was an adaptation mechanism for the body to function outside in response to physical stressors. Hypermetabolism can result from severity, types and treatment options of selected clinical conditions. Patients' preadmission status such as history of chronic diseases could further promote the hypermetabolic state. Proper metabolic assessment is prudent to identify these changes so that over or underfeeding in the very ill population can be prevented (Villet et al, 2003).

Flow phase refers to patients who have been adequately resuscitated, resumed hemodynamic stability and possessed adequate oxygen delivery. Catabolic activity dominates the *flow phase* and is driven by stress hormones such as cortisol, glucagon, insulin, growth hormone, catecholamine, and stress mediators such as prostaglandins, complement, and inflammatory cytokines. *Adaptive phase*, a sub-phase of *flow phase* then marks the beginning of anabolism and is associated with recovery.

F*low phase* can be prolonged by infection and recovery from surgery and results in chronic catabolism that leads to profound weight loss, negative nitrogen balance and recurring hyperglycemia (Cunneen and Cartwright, 2004).

Fung (2000) reviewed that hypermetabolism was common among those who suffered from trauma, burn, surgery, infections and inflammations. Cytokines is an inflammatory agent that is massively produced during critical illness and can aggravate hypermetabolic condition in patients. Therefore, Fung (2000) stated that real-time energy expenditure in patients during physical crisis could be greater than that calculated from predicted equations.

In summary, patients go through different metabolic changes according to their disease development. Resting energy expenditure has been observed to decrease during the more unstable *ebb phase* and progressively increased during recovery while in *flow phase*. Predicted equations are less applicable under the circumstances and actual measurement of energy expenditure should be considered.

Other Contributions to Total Energy Requirement In Critically Ill

Physical Activity

Physical activity can be negligible among the critically ill population because of the extent of injury, use of sedation and pain that can hinder movement and require total bed rest. Nevertheless, there are other related activities in intensive care that can mimic physical exercise and impose additional energy expenditure in the very ill patient population. Routine nursing care including bathing and turning, chest physiotherapy, ongoing procedures and examinations, medication of catabolic origin such as steroids can all mount up to considerable energy expenditure.

Miles (2006) reviewed that the direct relationship between physical stressors and energy expenditure was not well-defined. Author stated that energy expenditure increased in burn patients were contributed partially by elevation in muscular activity because of the injury rather than solely systemic stress. There was similar observation among patients with head trauma with increased muscular activity because of post-injury seizures, posturing and muscle hypertonicity that impact on their energy expenditure. Miles (2006) concluded in his systematic review that activity factor in very ill patients should be considered into the final calculation of energy expenditure even though there was no physical activity involved. Further studies should be conducted to investigate the relationship between energy expenditure and illness severity.

Dietary Thermogenesis

Enteral (tube feeding) and intravenous nutrition support (parenteral nutrition support) is common nutrition delivery methods in hospitalized patients. Alves and da Rocha (2009) studied 44 overweight or obese patients in the intensive care unit and a proportion of them were put on mechanical ventilation. Indirect calorimetry measurement was successfully performed on 29 patients during fasting state and fed state after achieving the estimated caloric goals. A mean duration of four days was required for patients to reach the estimated caloric goals through artificial feedings. Results showed that measured energy expenditure during fasting was 1798 ±495 kilocalories per day and after achieving caloric goals (fed state); their energy expenditure had increased to 1948 ±507 kilocalories per day. Energy expenditure was increased after patients had been fed. However, focus of this study was the agreement of measured energy expenditure to estimated equations, there was no

mentioning whether the difference in measured energy expenditure between fast and fed state was significant.

Cankayali, Demiraq, Kocabas, and Moral (2004) compared energy expenditure of 20 unconscious, mechanically ventilated patients in the intensive care unit. The patients received different types of amino acids at a randomly four-hour infusion interval at 0.4 gram per kilogram protein. 10 subjects received a standard amino acid solution and 10 subjects received a branched chain amino acid solution. Indirect calorimetry was performed to measure energy expenditure before infusion of amino acid solution infusion and every 30 minutes during the four-hour infusion period at 30, 60, 120 and 180 minutes until the infusion completed. Results indicated that there was significant increase in energy expenditure at 30, 150, 180 and 210 minutes in the standard amino acid solution group and the elevation extended to 240 minutes in the branch-chained amino acid solution group ($P<0.05$). The caloric load of the 2 amino acid preparations were the same and energy expenditure had indeed increased between fed and fasted state in intravenous nutrition support. Frankenfield and Ashcraft (2011) looked at 130 critically ill, mechanically ventilated patients with ischemic stroke, hemorrhagic stroke, isolated traumatic brain injury and traumatic brain injury with collateral injuries. Their resting metabolic rate was 2002 ±425 kilocalories per day for the unfed group and 1982 ±249 kilocalories per day for the fed ones and was not significantly different. The contradicting and inconsistent result observed from Frankenfield and Ashcraft (2011) demonstrated that determination of diet thermogenesis in the critically ill population was complex and difficult.

Medications

Energy expenditure in the critically ill population can either be aggravated

or attenuated by selected medications. Terao et al (2003) studied the effect of sedation on resting energy expenditure and oxygen consumption in patient population. Thirty-two surgical patients admitted for esophagectomy, with and without resection of malignant tumors of head and neck and dependent on mechanical ventilation were sedated postoperatively for at least 2 days. Ramsay sedation scale, body temperature and dosage of sedatives were evaluated at the time of indirect calorimetry measurement. Midazolam was the choice of intravenous sedative and was usually prescribed to patients in addition to analgesia (pain killers). Degree of sedation was categorized into light, moderate and heavy. Results showed that resting energy expenditure index (kilocalories per day per meter squared body surface area) was 865 ±105 compared to 1032 ±120 between heavy and light sedated groups and achieved statistical significance ($p<0.1$). Oxygen consumption was 125 ±16 and 151 ±18 milliliter per minute per meter squared body surface area in heavy and light sedated groups respectively and difference was significant ($p<0.1$). The heavier the sedation the lower energy expenditure was observed.

Mechanism of change in energy expenditure in relation to levels of sedation could be observed in Bruder et al (1998). Authors investigated body temperature and mean hourly energy expenditure among 24 patients with 13 of them in septic state and 11 were not. The patients were then divided into 3 groups to receive different levels of sedation and included 1 control group. There was significant and positive correlation between energy expenditure to basal energy expenditure ratio (EE/BEE) with different types of sedation ($p<0.0001$, $r^2 = 0.27$) but not with the control group. When core temperature was adjusted, EE/BEE was found to be the same among different levels of sedation except higher basal energy expenditure ratio was identified among septic than non-septic group. Energy

expenditure seems to vary among different levels of sedation due to changes in core temperatures. The positive effect of sepsis on energy expenditure however, remained the same even after adjustment of body temperature in this cohort.

Besides sedation, Miles (2006) also reviewed medications that were catabolic in nature including glucagon, catecholamine, growth hormone, and cortisol. This had been shown to acutely elevate resting energy expenditure. Ratheiser, Brillon, Campbell, and Matthews (1998) studied the effect of prolonged epinephrine infusion on resting energy expenditure of healthy individuals. Thirteen healthy men were infused with 23 hours of epinephrine to the high physiologic range (4720 ±340 pmol/L) after 24 hours of continuous saline infusion. Resting energy expenditure was significantly increased by 12% at the end of 23rd hour of epinephrine compared to saline infusion (97.5 ±kilojoules per kilogram per day vs 108.9 ±2.3 kilojoules per kilogram per day). Resting energy expenditure then returned to baseline 24 hours after epinephrine infusion had been discontinued.

Fever

Gore et al (2003) studied the association of fever and energy expenditure in burn pediatric patients. Eighty-four children were recruited with 40% or more burned total body surface area. They were then categorized from mild (39-39.4 degree Celsius) to severe (≥40 degree Celsius) fever using rectal temperature measurement. Results showed that resting energy expenditure compared to predicted equation was significantly increased in patients with (1.68 ±0.3) and without fever (1.38 ±0.39). The study demonstrated that energy expenditure increased with elevated body temperature. Authors mentioned that the additional benefit of better fever

control to weaken impact of hypermetabolic state among patients.

Definition of Sepsis

Members of the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference Committee (1992) defined sepsis as a clinical response with or without infection. Systemic inflammatory response syndrome (SIRS) is septic condition with ongoing inflammatory process independent of cause. Symptoms of SIRS included body temperature of more than 38 degree Celsius or less than 36 degree Celsius, tachypnea with respiratory rate of more than 20 breaths per minute or hyperventilation indicated by partial pressure of arterial carbon dioxide ($PaCO_2$) of less than 32 torr (less than 4.3 kPa), an alteration of white blood count of either more than 12000 cells per mm cube or less than 4000 cells per mm cube or the presence of more than 10% immature neutrophils. Sepsis relates to systemic inflammatory response syndrome with a confirmed infectious source.

Sepsis induces complex physiological stress response among the critically ill population with high mortality rate. The cascade of metabolic events in sepsis depends on site of infection and characterizes by redness, pain, heat, swelling, and loss of functions in the early days. A patient presents with at least two of the following general SIRS criteria is deemed septic; abnormal body temperature (hypo- or hyperthermia), elevated heart and respiratory rates, and altered white blood cell count. Severe sepsis is the involvement of more than one septic organ and septic shock is severe sepsis with cardiovascular dysfunction and does not respond to fluid resuscitation. Patients receive inotropic or vasopressor agents even without hypotension will still be considered to have experienced septic shock. The pathophysiology of sepsis is usually progressive and caused by any number of pathogens including bacteria, yeasts, viruses, and/or parasites. The end

result is often multiple organ dysfunction syndrome and death (Cunnen and Cartwright, 2004).

Metabolic Alteration In Sepsis

Metabolic response differs with severity of sepsis. Kreymann (1993) demonstrated that different severity of sepsis was associated with further reduction of oxygen consumption. A total of 30 patients were divided into sepsis (complicated), sepsis syndrome (non-complicated) and septic shock (critical). Carbon dioxide production and oxygen consumption were measured and resting energy expenditure was calculated using Weir's equation. Resting metabolic rate was defined as the percentage of measured resting energy expenditure over calculation from Harris-Benedict equation. Results showed that the mean resting metabolic rate in sepsis was 55 ±14%, sepsis syndrome was 24 ±12% and septic shock was 2 ±24% ($p < 0.001$). Mean resting metabolic rate was lower in uncomplicated sepsis (sepsis syndrome) than complicated ones (sepsis). Patients with septic shock experienced mean resting energy rate closed to healthy individuals (2 ±24%). The more severe the septic condition was, the lower the resting metabolic rate according to Kreymann (1993). In addition, Dickerson, Vehe, Mullen, and Feurer (1991) examined 40 patients with either acute pancreatitis, chronic pancreatitis or acute pancreatitis complicated by sepsis or non-sepsis prospectively. Resting energy expenditure measured by indirect calorimetry compared to predicted equation was significantly greater ($p < 0.02$) in patients with pancreatitis with septic complication (120 ±11%) than the non-septic group (105 ±14%). Uehara, Plank, and Hill (1999) studied energy expenditure in critically ill patients with sepsis and trauma during the initial 2 weeks of admission into intensive care. Twelve severely septic and 12 trauma patients were recruited. Resting energy expenditure was measured on daily basis for 2

weeks. Results showed that resting energy expenditure gradually increased during first week after onset of severe sepsis or major trauma (37 ±6% of predicted equation) and was highest during second week (60 ±13% of predicted equation). During the second week patients in severe sepsis and trauma groups had higher resting energy expenditure (3257 ±370 kilocalories per day vs 1927 ±370 kilocalories per day) than the previous week. These studies showed that occurrence, severity and duration of sepsis could elevate energy expenditure in the very ill patient population despite of their primary diagnosis.

Energy expenditure was also observed to be higher among survivors in intensive care. Carré et al (2010) examined change of mitochondria (energy production within a cell) morphology and the relevant energy and substrate production during critical illness. Mitochondrial protein content and phosphorylated (energy) metabolites were measured among 16 critically ill patients. Ten of the 16 patients survived in the intensive care and results indicated that mitochondrial size increased in non-survivors but survivors had higher muscle adenosine triphosphate (ATP) content compared to non-survivors.

Substrate Utilization In Sepsis

Alteration in glucose metabolism was observed in the very ill population because of increase glucose production driven by gluconeogenesis and insulin resistance induced by stress hormones. Increase glucose production and decrease glucose uptake led to hyperglycemia (high blood glucose). Simultaneously, peripheral fat was broken down and free fatty acids were released into the bloodstream that exceeded its oxidation rate. The excess serum fatty acids were then re-esterified in the liver and elevated hepatic triglyceride accumulation. The pathway of free fatty acid

re-esterification into triglyceride is a futile cycle with additional energy need. The feedback loop of lipid re-esterification results in more lipolysis and energy demand (Wolfe, 1997).

Martinez et al (2003) studied metabolic changes and tissue lipolysis during metabolic stress process among critically ill patients with septic condition, circulatory failure and healthy individuals. Whole body substrate utilization, adipose tissues lactate and glycerol releases (index of adipose tissue lipolysis) were used as indicators. A group of 7 healthy human volunteers and 2 groups of each with 5 critically ill patients were separated into severe sepsis or septic shock. Another group of 6 patients from post-cardiac surgery under extracorporal bypass for circulatory failure were also recruited. Results showed that energy expenditure was highest in the septic group followed by the healthy group and the circulatory failure group (1710 vs 1640 vs 1390 kilocalories per day). The net glucose (6.1 vs 4.3 vs 1.75 micro-mole per kilogram per minute) and lipid oxidation (1.26 vs 0.89 vs 0.6 milligram per kilogram per minute) were also highest in both septic groups followed by healthy control and the circulatory failure group. Authors explained that the increase reliance on gluconeogenesis was responsible for an increase glucose production. Lipid transport in septic condition could be altered and modulated by cytokines but the relationship remained to be established.

Jeevanandam, Young, and Schiller (1990) investigated lipid mobilization and utilization pattern in the critically illness population. Nine adult patients admitted to intensive care setting with severe trauma were recruited and indirect calorimetry was performed once during fasting and within 48-96 hours after admission to the intensive care. A glucose-based intravenous nutrition was commenced and continued for the next 5 to 7

days. Results showed that glucose-based calories reduced but not normalized lipid utilization cycle. A total of 47 ±7% of fat being mobilized was recycled to store as triglyceride and increased to 54 ±9% after nutrition support was provided. The energy demand of this lipid cycle was 38 kilocalories per day; five times that of normal individuals and corresponds to 1.34% of resting energy expenditure.

Weissman et al (1986) also studied substrate utilization of 15 mechanically ventilated critically ill patients. They were either provided with minimal of 500 kilocalories per day in the form of intravenous dextrose or normal saline (non-caloric) both for 8 hours. Indirect calorimetry measurement was performed on the patients during rest (lying motionless with eyes open and responsive to surrounding events), activity (all other situations not considered rest or sleep) and sleep (not aroused by surrounding events). Lipid utilization was found to be higher than carbohydrates in this cohort during activity (respiratory quotient 0.75 ± 0.02) than both rest and sleep (respiratory quotient 0.78 ±0.01). Nonetheless, the report was brief and there was no detail account of the calculation methodology on substrate utilization. Protein metabolism was not a focus in this study due to numerous reviews of its insignificant impact on energy expenditure. Furthermore, urinary nitrogen was not collected in this cohort for nitrogen balance test.

Consequences of Energy Mismatch In the Critically Ill

Faisy et al (2011) studied impact of early nutrition support on patients in the intensive care and their subsequent energy balances with the occurrence of specific pathogens that was responsible for causing ventilator-associated pneumonia (VAP). This was a prospective, observational and cohort study. Energy balance was compared to the microbiologic results of the specific

fiber-optic BAL cultures of 76 patients who were relying on ≥96 hours of mechanical ventilation and developed VAP during their stay in intensive care. There were 22 cultures out of the 76 tested significant with Staphylococcus aureus (S aureus) concentration, a specific pathogen that led to development of VAP. The higher accumulative energy deficit in patients was associated with the specific S aureus VAP compared to other pathogens (-10275 ±4211 kilocalories vs -7376 ±4013 kilocalories from intensive care admission to day of culture obtained and $p < 0.1$). The study also demonstrated a positive correlation between energy deficit and higher rate of specific strain that caused the VAP.

Rubinson et al (2004) also conducted a prospective cohort study to examine the association of caloric provision and risk of nosocomial bloodstream infection in patients admitted into the medical intensive care unit at Johns Hopkins Hospitals. The primary outcome was nosocomial Bloodstream Infection Indicator (BSI) and its correlation with caloric intake. Results showed that patients who received >25% of recommended caloric intake was associated with significantly lower risk of bloodstream infection (relative hazard, 0.24; 95% confidence interval, 0.10–0.60) when compared to those receiving <25% even after adjustment for Simplified Acute Physiology Score II (SAPSII).

Villet et al (2003) stated that energy deficit occurred during the first week of stay in the intensive care unit could not be compensated by nutrition support for the remaining stay in intensive care unit. Authors conducted a prospective observational study among patients who stayed in the intensive care for 5 or more consecutive days. Energy expenditure was measured on a total of 48 patients by indirect calorimetry. Total energy was provided by tube feeding combined with intravenous nutrition support.

Energy balance was calculated by weekly accumulation from week 1 to 4 after admission. Results showed that total accumulated energy deficit was -12600 ±10520 kcal and was significantly correlated with infectious complications ($p<0.001$) which occurred only after one week of admission. It was arguable that correlation was not equal to causality due to obvious relation for patients in the intensive care to experience complications during course of disease development. In addition, the most severely ill patients were most difficult to be fed by tubes and experienced intolerance. The strongest support for the negative correlation between negative energy balance and clinical complication was that timeframe it occurred at the end of first week of stay in the intensive care. Authors emphasized that the accumulation of energy deficit for only one week in the very ill population was associated with adverse health outcomes including systemic organ and respiratory failure.

Kan et al (2003) studied the relationship of energy requirement and selected clinical outcomes in a cohort in the intensive care dependent on mechanical ventilation. Fifty-four patients were divided into three groups including underfeeding, adequate feeding and overfeeding. Clinical outcomes were APACHEII score, length of stay in the intensive care and duration on mechanical ventilation. Results indicated that only duration on mechanical ventilation was significantly and positively correlated with the adequate feeding group ($r=0.525$, $p<0.05$).

The impact on clinical outcomes is often multifactorial and difficult to single out nutrition as the most influential. Fontaine and Muller (2011) reviewed that underfeeding was common practice and often desirable in the intensive care setting due to optimization of blood glucose. It is actually patients under stress who trigger cascade of stress-related hormonal

production. The subsequent effect of these catabolic hormones promotes insulin resistance and results in increase blood glucose level. It is also common belief of intensivists that underfeeding could blunt the hypermetabolic development of critically ill patients. Fontaine and Muller (2011) emphasized that there was no evidence to indicate underfeeding could alleviate hypermetabolism in the critically ill population but further worsen malnutrition.

Metabolic Requirement and Respiration

Healthy people seldom realize the effort to breathe. Breathing is a normal mechanical process that requires minimal metabolic effort in the healthy population. Respiratory muscles including diaphragm and intercostal muscles between the ribcage are actively engaged in the ventilation mechanism. Diaphragmatic fatigue contributes to respiratory failure. Nonetheless, this work of breathing for critically ill patients can be energy-costing. Muscular atrophy as a result of malnutrition predisposes patients to develop fatigue and suboptimal respiration as well as prolong duration on mechanical ventilation. Energy expenditure during respiration mainly contributes to work of breathing (minute ventilation compliance and resistance), efficiency (lung volume, neuromuscular disease, nutritional status and body position), and energy supply in oxygen transport, oxygen content, blood flow, substrate availability, and substrate stores (McArdle et al, 1996).

The relationship between nutrition and ventilatory drive is dynamic. The demand for energy increases with increasing level of respiratory muscular activity in response to oxygen consumption and carbon dioxide production. The hypermetabolic condition during illness further increases respiratory activity to promote oxygen uptake for nutrient metabolism and adequate

respiration. Under-nutrition leads to loss of diaphragmatic muscle mass and prevents disruption of normal breathing mechanism. Refeeding in malnourished individuals can preserve muscle mass and improve ventilatory response. Adequate nutrition secures energy supply for patients to maintain respiration by preserving vital respiratory muscles, preventing muscular atrophy and reducing muscular fatigue (Askanazi et al, 1982).

Benotti and Bistrian (1989) explained that malnutrition impaired respiratory muscle function and reduced alveolar ventilation and resulted in excess carbon dioxide production (hypercapnia). Work of respiratory muscle will have to increase to compensate for the severe ventilation hyperperfusion mismatch (hypoxia and hypercapnia). Therefore, adequate nutrition support is crucial to meet the energy demand for maintaining work of breathing and promoting homeostasis in the respiratory and circulatory systems. Authors stated that prolonged length of stay as well as mortality and morbidity were common among hospitalized and malnourished patients.

Artinian, Krayem and DiGiovine (2006) conducted a study to observe impact of early feeding on clinical outcome among mechanically ventilated patients in the intensive care. A total of 4049 patients requiring mechanical ventilation for more than 2 days in intensive care were recruited. They were divided into the early enteral nutrition (<48 hours after initiation of mechanical ventilation) and non-early feeding group. Results indicated that intensive care mortality was 18.1% in the early feeding group versus 21.4% in the non-early feeding group ($p=0.01$). Hospital mortality was 28.7% in the early feeding group and 33.5% in the non-early feeding group ($p=0.001$). It is arguable that the early feeding group can potentially

receive longer duration of nutrition support and more likely to reach their nutrition goals. On the other hand, non-early feeding group can also be patients with more severe clinical conditions and thus, they are not indicated to initiate feeding until a later stage. These patients can also have high risk of mortality.

Dias et al (2004) conducted an animal study to examine the influence of malnutrition on lung and chest wall elastic and resistive pressure. Resistive pressure contributes to the mechanical changes in respiration including activation and inactivation of respiratory muscles. Mechanical changes in relation to histology in respiration were also studied. Twenty-four rats were divided into control and nutritionally deprived groups. Results showed that tidal volumes, minute ventilation and mean inspiratory flow were lower and inspiratory duration was longer in the nutritionally deprived group. Photomicrographs of lung parenchyma showed that the nutritionally deprived group had hyperinflated alveoli with patchy atelectasis, interstitial edema, inflammation and diaphragm and inter-costal muscles were atrophied. Adequate nutrition support is important to promote the anatomical and functional health of respiratory system.

Metabolic Requirement and Mechanical Ventilation

On the other hand, studies were conflicting about metabolic requirement of patients when they were also relying on mechanical ventilation. Matching energy intake and expenditure is important for the critically ill to promote recovery as well as weaning from mechanical ventilation. Under-nutrition can impair regeneration of respiratory epithelium, limit functionality of respiratory muscles, and thus, prolong mechanical ventilation (Kan et al, 2003). Conversely, sustained overfeeding can cause liver dysfunction

with fatty infiltration, hyperglycemia and excess carbon dioxide production that can collectively delay weaning from mechanical ventilation. In a study by Reid (2006) on critically ill and mechanical ventilated patient in the intensive care unit, overfeeding and underfeeding were defined as more than 110% and less than 80% of estimated energy requirement respectively and adequate feeding was defined as 80-110% estimated requirement. Patients received adequate feeding only on 30% of their average length of study (mean length of stay was 97 days). In other words, these patients were either over- or underfed majority of their stay in the intensive care (Fontaine and Müller, 2011). Metabolic assessment of the very ill and mechanical ventilation-dependent patients remains a challenge.

Metabolic cost of respiration in patients was demonstrated by Ireton-Jones et al (1992). Authors measured energy expenditure in 200 patients divided into spontaneous breathers and dependents of mechanical ventilation. Results showed that patients on mechanical ventilation had significantly ($p<0.001$) higher measured energy expenditure (2349 ±764 kilocalories per day) than the self-breathers (1747 ±654 kilocalories per day). Besides the existence of mechanical ventilation, modes of ventilatory support can also be energy-demanding. Stocker and Biro (2005) studied different modes of mechanical ventilation. Various ventilator modes generate and regulate gas flow, supply oxygen into the lungs at desired volume and maintain airway pressure for respiratory function for patients. Partially-assisted mechanical ventilation support requires patients to initiate partial self-breathing and the remaining support comes from the ventilator. On the other hand, patients on spontaneous breathing are required to contribute to the entire breathing mechanism.

Hoher, Teixeira, Hertz and Moreira (2008) studied energy expenditure of

100 mechanically-ventilated patients in the intensive care unit receiving controlled or assisted breathing support. Results showed that patients on controlled ventilator mode expended approximately 10% fewer calories than the assisted breathing modes (1712.76 ±491.95 vs 1867.33 ±542.67 kilocalories per 24 hours and $p<0.001$). Authors explained that patients on assisted breathing mode required additional energy for self-breathing to reach the sensitivity threshold of the ventilator for the positive pressure support to kick in and complete the respiration. The extra 10% of energy expended identified in this cohort during assisted ventilatory mode was in accordance to the deviation with predicted equation. Therefore, Hoher et al (2008) proposed to add a 10% adjustment factor into the predicted equation for patients on partially-assisted ventilatory support.

The conflicting results between Ireton-Jones (1992) and Hoher et al (2008) can be contributed by use of different research methodologies, heterogeneous nature of patients, provision of non-standardized nutrition support regimens, and the use of various dosages and types of vasoactive drugs and heavy sedation.

Metabolic Alteration Upon Liberation From Mechanical Ventilation

There was scarce study to demonstrate impact of weaning from mechanical ventilator on metabolic requirement of patients. Taggert et al (2000) explained in a case report that the common technique to wean patients from mechanical ventilation was to strengthen the atrophied respiratory muscles through a repeated "work" and "rest" cycle on mechanical ventilation. The "work" and "rest" technique is based on allowing respiratory muscles to rest adequately by providing some degree of mechanical ventilation support to allow self-breathing begins again in a less fatigue state. Respiratory muscle fatigue is the loss of force from the respiratory muscles

due to excessive work of breathing or inadequate rest. The alternate "work" and "rest" cycle from weaning mechanical ventilation could prolong time to fatigue and increased duration to weaning from the ventilator. Increase in work of breathing and gas exchange can contribute to respiratory muscle fatigue. Bellani et al (2010) studied the relation between oxygen consumption and patients who successfully weaned from mechanical ventilation. A total of 28 patients with respiratory failure on mechanical ventilation were recruited. Oxygen consumption level was measured during the weaning process with descending levels of positive pressure support from the mechanical ventilator. A total of 12 patients failed the weaning trial in the end. These patients were observed to experience significantly higher minimum oxygen consumption compared to those who successfully weaned from mechanical ventilation (215 ±53 vs. 174 ±44 milliliters per minute and $p<0.05$). Study showed that there was obvious interaction between mechanical ventilatory drive and amount of oxygen consumed. Bellani et al (2010) stated that the success of weaning from mechanical ventilation could be driven by the ability of respiratory system to function properly and patients' tolerance to increase work of breathing as ventilatory support decreased.

In the case report by Taggert et al (2000), the particular patient had consistently failed to wean from mechanical ventilation on Day 4 of the weaning trial post-operatively. Indirect calorimetry measurement revealed that the energy expenditure of this patient was gradually elevating through each "work" and "work" cycle of weaning, despite even when the work of breathing and energy expenditure returned to baseline.

Muscle fatigue occurs when there is no consistent daily repletion of muscle

glycogen. Body will have to rely on liver gluconeogenesis (producing energy from non-glucose source) for energy source; however, this process produces glycogen at a much slower rate. Inadequate nutrition couples with increase energy demand, the glycogen being produced from the liver will be prioritized to other vital organs for survival rather than for restoring function of the respiratory muscles. Hence, patients who possess suboptimal respiratory function develop will prolong their reliance on mechanical ventilation. On the contrary, Huie-Chen, Ching-Hsiuang, and Ling-Jang (2005) studied the effect of feeding levels and clinical outcomes on 28 stable patients on mechanical ventilation. Patients were divided into two groups and provided with calories in the form of tube feeding that was equivalent to 1.2-fold (isocaloric) and 1.8-fold (hypercaloric) of resting energy expenditure. The hypercaloric group had significantly higher carbon dioxide production in 4 weeks compared to those receiving isocaloric feeding. Consequently, the excessive carbon dioxide production can add burden to patients' respiratory cycles. Hence, optimal nutrition support is prudent to promote respiratory tolerance and facilitate liberation from mechanical ventilation.

Predicted Versus Measured Energy Expenditure Among the Very Ill

The National Academy of Sciences, Institute of Medicine (IOM) and Food and Nutrition Board in partnership with Health Canada had developed an estimation of energy requirement for men, women, children and infants and pregnancy and lactating women. The estimation of energy requirement incorporated age, weight, height, gender, and level of physical activity for people ages 3 years and older. Additional calories for tissue growth in infants and young children, as well as pregnant and lactating females were also included, thus, estimation of energy requirement was more superior to recommendations that only based on healthy population without taking into

account of the physiological factors such as physical activity level, lifestyle, stressors, etc.

Currently more than 190 equations had been developed. The earliest and most familiar would be the Harris-Benedict equation which was being developed in 1919. Nonetheless, these predicted equations had been shown to possess poor agreement with results from measured energy expenditure. Savard et al (2008) studied the agreement between predicted equations and measured values from indirect calorimetry commonly used in 45 critically ill and ventilator-dependent patients. There was a moderately strong positive correlation between predicted equations with measured values ($r=0.62$, $p<0.001$). Bland-Altman analysis demonstrated mean bias of -192 ±277 kilocalories per day with limits of agreement ranged from -735 to 351 kilocalories per day among the selected predicted equations. The deviation of predicated and measured energy expenditure could be diminution of metabolic activity related to prescription of sedatives, catecholamine and vasopressors as well as changes in body mass and aging of patients in the intensive that could impact significantly on resting energy expenditure. Kross et al (2012) conducted similar study among 970 obese critically ill and mechanical ventilation patients. There was only agreement between selected predicted equations and measured energy expenditure in designated weight groups. The application of predicted equations among patients with different weight categories could also be difficult.

Predictive equations often exclude variability of metabolic response to injuries which is an inherent flaw in estimating energy expenditure. The concept of patients being able to demonstrate predictable, uniform and singular metabolic response to a given disease process was not realistic or

practical. Therefore, predicted equations can only be as close to measured values base on the variables being incorporated. Frankenfield, Ashcraft, and Galvan (2012) studied the metabolism of hemorrhagic stroke compared to traumatic brain injury. One hundred and thirty patients with ischemic stroke, hemorrhagic stroke, and isolated traumatic brain injury or traumatic brain injury with collateral injuries were recruited to measure their energy expenditure and compared to selected predicted equations. They were all on mechanical ventilation and prescribed with various types and levels of inotropes and sedatives. Extent of hypermetabolism was different with different clinical diagnoses after correction of sedation level and fever. Predict equations to estimate energy expenditure was closer to measured values only 72% of the time. Frankenfield et al (2012) stated that body mass, fever and minute ventilation could explain most of the deviation between measured and predicted energy expenditure.

In addition, extreme circumstances such as obesity and fluid resuscitation further complicate the use of equations and led to tendency for overfeeding. McClave, Kleber, and Lowen (1999) reviewed that septic patients with peritonitis could retain an average of 12 liters of water after volume resuscitation to stable their conditions. The actual weight of these patients gradually returned to normal when the excess resuscitative water was excreted. The excess fluid could impact on calculating energy expenditure unpredictably. Individuals with extreme body mass led to confusion about whether the excess weight was entirely fat or fat-free mass (muscles) that was metabolically active in nature for determining the most appropriate body weight for calculating energy expenditure. The inherent flaw is the application of predicted equations in a narrowly defined population to any heterogeneous patient population. The lack of individuality in these predicted equations further complicates the true

energy requirement of the very ill population.

One of the reasons for the poor prediction from estimated equations was because of the unreliable body mass among critically ill patients. Krenitsky (2004) stated that the application of adjusted body weight was based on the idea of a certain percentage of excess body weight in obese individuals was not all fat but contained a certain percentage of muscles which was metabolically active. This additional estimation of muscle weight was added into the ideal body weight of the obese individual and referred to as adjusted body weight. By using the adjusted body weight to estimate energy expenditure, the gap between under or overestimating energy expenditure in obese patients can be narrowed. Furthermore, body mass adjustment for fluid resuscitation, peripheral edema, etc. can minimize introduction of error into calculation of energy expenditure using predicted equations.

Adjustment Factors To Determine Energy Expenditure In the Very Ill Population

In the intensive care setting, patients are mostly bedridden and thus, the estimated energy expenditure can be similar to total energy expenditure. In other words, patients' measured energy expenditure should closely resemble the daily total energy expenditure. Nevertheless, when patients start to ambulate and progress to other daily activities towards recovery, total energy expenditure will no longer account for only resting metabolic rate. Total energy expenditure should adequately reflect patients' daily requirement by including resting energy expenditure and daily physical activity (da Rocha, 2006 and Porter, 2006). These additional energy costs for daily care and rehabilitation should be included into total energy

expenditure as well.

Fung (2000) stated that accurate calculation of energy expenditure in critically ill patients using predicted equations was difficult hence, clinicians and dietitians often provide inappropriate nutrition support to patients. A device to measure real-time energy expenditure can become an invaluable option. Individualized metabolic assessment and tailor-made nutrition support regimen are vital to optimize nutrition for critically ill patients.

Miles (2006) conducted a systematic review of 19 studies on resting energy expenditure measured by indirect calorimetry against estimated basal energy expenditure calculated from Harris-Benedict equation. They included postoperative patients with trauma, sepsis, cancer, pulmonary disease, cardiovascular disease or other miscellaneous or unspecified clinical diagnosis. The average resting measured energy expenditure was 113% of the calculated values. Author suggested that overfeeding might contribute to thermogenic effect of food and resulted in higher resting energy expenditure. Weissman et al (1986) recruited 45 critically ill patients for postoperative resting energy expenditure measurements. They were also hemodynamically stable, non-comatose and receiving mechanical ventilation. The measured values were compared to predicted formulas such as Harris-Benedict and Aub-Dubois formulas. Measured values differed 70 to 140% from predicted equations. Authors stated that there could numerous complex factors that impact on patients' metabolic rate during critically ill condition.

MacDonald and Hildebrandt (2003) compared the agreement of five predicted equations against measured energy expenditure among the critically ill population. They discovered that selected predicted equations

with adjusted stress factors could only fall within an acceptable range from measured values in equal to or more than 80% of the time. The selected predicted equations in the study, with incorporation of specific stress factors might be able to replace indirect calorimetry measurement in a narrowly-defined population. Due to volatile clinical conditions and heterogeneity of the chosen patient population, the authors recommended that clinicians should revisit these predicted equations regularly by comparing to measured values. McClave et al (1999) stated that a sick individual with same diagnosis could have various complications and different disease severity. Therefore, these patients could experience hypo-, normo- or hypermetabolic with the same disease condition.

Nonetheless, Brandi et al (1999) demonstrated that disease severity did not impact on measured energy expenditure of patients. Authors studied 26 energy expenditure of mechanically ventilated multiple trauma patients. They investigated the correlation between injury severities, energy expenditure calculated from Harris-Benedict equation with adjustment factors for trauma and measured results from indirect calorimetry. Results indicated that there was no statistically significant correlation between both calculated and measured resting energy expenditure with the Injury Severity Score (ISS). Injury Severity Score is a set of scoring system being developed to closely correlated severity and mortality of patients with multiple injuries (Baker, O'Neill, Haddon and Long, 1974). Brandi et al (1999) stated that the calculation of total energy expenditure should include other foreseeable variables including heart rate and minute ventilation.

Boulanger, Nayman, McLean, Philips and Rizoli (1994) also showed that there was no correlation between Injury Severity Score and measured

energy expenditure in adult blunt trauma patients on mechanical ventilation. A total of 115 patients were recruited with their energy expenditure both measured by indirect calorimetry and calculated using Harris-Benedict equation. Only Harris-Benedict equation, age, height, weight, sex, temperature, and use of paralytic agents showed significant correlation with measured energy expenditure. Finestone, Greene-Finestone, Foley, and Woodbury (2003) observed similar phenomena in a group of patients with different severity of stroke. They examined the impact of stroke size, type, location, severity and energy expenditure and tried to develop a factor for estimating energy expenditure using Harris-Benedict equation. Ninety-one patients and 73% of them were measured a total of 3 times across the duration of stay in the stroke unit. Resting energy expenditure and the association with stroke size, type, location, and severity and evaluate were observed and used to develop additional stress factors to adjust the predicted energy expenditure equation for the cohort. Indirect calorimetry measurement was performed at designated intervals on patients and the measured energy expenditure was compared against predicted equation. Measured resting energy expenditure after stroke in the cohort varied significantly not because of stroke type or size but the concomitant occurrence of infection or other complications.

Frankenfield et al (2004) estimated energy expenditure using selected predicted equations on 47 critically ill patients. The estimated values were then compared to measured energy expenditure by indirect calorimetry. The subjects were mechanically ventilated surgical, trauma, and medical patients. Tube feeding was maintained during the test and thermogenic effect of food was equally applied to all subjects. The authors concluded that the different estimated equations for energy expenditure must be considered strategically due to the narrow application

in an array of clinical conditions. MacDonald and Hildebrandt (2003) also stated that predicted equations with adjusted stress factors were only achieving 10-20% variance from measured results 80% of the time. Predicted equations with specific stress factors adjustment for estimating energy expenditure may be able to replace measured energy expenditure in a narrowly-defined population. Furthermore, Dickerson, Vehe, Mullen and Feurer (1991) performed resting energy expenditure measurement in hospitalized patients with pancreatitis and found that patients with septic pancreatitis had the largest margin of deviation (77-139%) from Harris-Benedict equation in estimating energy expenditure. The authors stated that the septic component could be a decisive factor in affecting resting energy expenditure among patients with pancreatitis. The study also indicated that there was a wide margin of variation between predicted and measured energy expenditure in this population.

Brandi et al (1997) reviewed that predictive equations became increasingly inaccurate especially in critically ill patients who had prolonged intensive care stay. These patients were at high risk of developing organ dysfunction and eventually death and their nutritional status deteriorated due to persistent stage of catabolism. Brandi et al (1997) stated that routine practice in assessing energy expenditure in critically ill patients was by the predicted equations multiplied by an activity and stress factor. These stress and activity factors are often proportionate to patients' pathologic conditions and level of physical activity.

In summary, the use of adjusted stress factors in predicted equations to calculate energy expenditure is highly questionable. Patients with critically illness are often sedated, dependent on artificial ventilation and progress differently in their acute conditions, complications and therapies.

Indirect calorimetry measurement can provide metabolic information despite variability of daily energy expenditure within individual patient due to complications, infections and therapeutic procedures.

Chapter 4: Introduction of Metabolic Assessment

Metabolic assessment is important for clinicians to acquire knowledge to provide optimal nutrition support for patients. Factors that affect energy expenditure as mentioned in previous chapters can markedly impact on accuracy of the assessment. Since predicted equations were shown to result in significant margin of error and development of reliable estimated equations needs to compare to some gold standards, different metabolic devices have been developed for such purposes. (This chapter provides an overview of different methods to measure energy expenditure.

Calorimetry

Calorimetry is the quantitative measurement of heat requirement during a chemical process. A calorimeter is the instrument or device to measure heat requirement for the process (http://www.chem.ufl.edu/~itl/2045/lectures/lec_9.html). Calorimetry can be categorized into direct and indirect as well as the device (calorimeter) to measure energy expenditure can be described as opened or closed.

Direct Calorimetry

Direct calorimetry measures total heat loss from the body. Participants are placed in a thermally-isolated structure and individual body heat dissipation is measured accurately. The structure must be large enough to accommodate moderate activity of daily living and it is sometimes named as whole room calorimeter. Resting energy expenditure will be measured as a form of heat dissipation. The heat being generated by individuals inside the testing structure will be a summation of oxidation from carbohydrates, fat and protein. This methodology does not allow differentiation of substrates used during energy production. This form of calorimetry study is limited to confinement and not as a simulation of

free-living environment. The applicability of this method is limited by cost and complex engineering and operation due to lack of appropriate facilities (Frary and Johnson, 2000). Even though direct calorimetry is the most direct and accurate way to obtain measured energy expenditure, it is impractical in clinical setting with environmental and patients' selection constraints (Ainslie, Reilly, and Westerterp, 2003).

Indirect Calorimetry

Indirect calorimetry on the other hand, obtains resting energy expenditure through measuring gas exchanges from either a mix chamber or a breath-by-breath device. Indirect calorimeter obtains total energy production through collection of oxygen consumption and (carbon dioxide production). The underlying assumption is total oxidation of ingested nutrients results in the production of carbon dioxide (Ainslie et al, 2003).

Brandi, Bertolini, and Calafa (1996) stated that human body was similar to a furnace burning fuels (carbohydrate, protein and fat) and in the process produced carbon dioxide, water and nitrogen. It is based on the assumption that oxygen is completely and rapidly oxidized during the process. This is because oxygen diffuses rapidly at the cellular level and body pool under resting is very small. Therefore, any variation in oxidation should equal to variation in the oxygen concentration being utilized. Second assumption of indirect calorimetry is that all expired carbon dioxide should be derived only from complete oxidation of fuels (carbohydrate, protein and fat) in the absence of any transit delay between cells and expired gas. This usually takes place during steady-state condition of patients meaning no abrupt or rapid change in ventilation, acid base status (bicarbonate pool) and the metabolic production of carbon dioxide. In other words, all the nitrogen being produced from protein

oxidation is precisely measured in the urine. This takes place when renal function is normal, urine collection is precise and gluconeogenesis (production of glucose from non-glucose source) from protein is insignificant. In addition, nitrogen pool in the body is relatively large and thus, able to buffer sudden changes in nitrogen production and delay the corresponding changes in urine nitrogen excretion. In practice, duration of urine collection must be adequate in order to reflect the belated changes.

Indirect calorimetry can be classified according to the method of measurement and applied to both open and closed-system. Inspired and expired concentration of oxygen, carbon dioxide and inspired and expired minute ventilation are required to calculate energy requirement through calorimetry measurement. Temperature and pressure must also be obtained manually because most gas analyzers can only measure partial pressure of gases. Nonetheless, indirect calorimeters have recently been manufactured into more portable units. Individuals will commonly breathe into a mouthpiece or ventilated hood and their expired gases are collected. Modern indirect calorimeter is popular for its maneuverability and lower equipment cost compared to traditional indirect and direct calorimeters. Measuring devices including canopy respirator or ventilated hood is useful for both short and long term measurements. A controlled laboratory setting will be indicated if the measurements are relevant to energy requirement for specific physical activity. Otherwise, a bedside mobile metabolic cart can be applicable in clinical setting to obtain patients' daily measured energy expenditure. The values of the expired gases are converted into kilocalories of heat produced per square meter of body surface per hour and can be extrapolated to energy expenditure in 24 hours.

Porter (2006) reviewed basic assumptions of indirect calorimetry:

- Complete oxidation of carbohydrates, protein and fat into carbon dioxide, water, urea and adenosine triphosphate in the body was expected. Nevertheless, energy being generated through other metabolic pathways such as lipogenesis (production of fats) and ketogenesis (production of ketones) were not considered. Lipogenesis is common in patients who are overfed with carbohydrates and can elevate oxygen consumption and carbon dioxide production compare to ketogenesis which will be similar to same gas exchange mechanism.

- Substrates deposition in tissues during anabolism or growth did not contribute to oxygen consumption and carbon dioxide production. Energy for growth can be markedly higher than the measured energy expenditure. The potential energy for anabolism was estimated to represent 24 to 31.5% of total energy expenditure in very small infant.

- The relationship between oxygen consumption and carbon dioxide production should be direct, however, when the pool of carbon dioxide in peripheral tissues temporarily increases due to clinical condition such as decreased heart rate and frequent adjustment of ventilator setting could increase or decrease minute ventilation and temporarily affect carbon dioxide balance in the body. The body then increased alveolar ventilation to eliminate the excess carbon dioxide to induce metabolic alkalosis and same with metabolic alkalinity which was compensated by the body decreased alveolar elimination of carbon dioxide. These clinical changes could lead to large margin of errors in measuring resting energy expenditure using indirect calorimetry (Porter, 1996).

- In addition, measured resting energy expenditure did not account for energy loss from nasogastric aspirate, wound drainage, fistula outputs

and/or hemofiltration. Glycosuria led to significant energy loss if glycemic control is unsatisfactory even with accurately measured results (Fontaine and Muller, 2011).

The mathematical model of indirect calorimetry is the amount of energy liberated as heat when 1 molecule of one of the three main fuels (carbohydrate, protein and fat) is being oxidized in a calorimetric bomb. Indirect calorimetry measurement bases on the assumption that energy produces by fuel oxidation is equivalent to the heat releases by fuel combustion. Glucose, fat and protein oxidized in the body are derived from the values of oxygen consumption and carbon dioxide production as well as urinary nitrogen to calculate per gram of substrate being oxidized. When the oxidative rate of glucose, lipid and protein have been calculated, energy expenditure can then be obtained from the caloric equivalent of the three substrates. Urinary nitrogen excretion measurement is not mandatory for energy expenditure estimation. The error of neglecting the urinary nitrogen measurement produces an error of only 1-2 % in the true energy expenditure and <4% in studies among the critically ill population (Brandi et al, 1996).

Open-circuit calorimetry

Open-circuit indirect calorimetry is often deemed more suitable to measure energy expenditure during exercise. Flow-through technique allows large volume of outside air to pass through a hood worn by the participant. Patients will expire and inspire into the air-stream inside the hood and airflow and percentage of oxygen and carbon dioxide are measured precisely to calculate gas consumption as well as respiratory exchange ratio. The flow-through type of open-circuit calorimeter is useful for long-term measurements with study participant either at rest or performing light

exercise. Douglas bag is another well-known open-circuit calorimeter in which individual will inspire outside air through a mask or mouthpiece containing a one-way valve and expires into the bag. The volume of air in the bag is measured to calculate minute ventilation (Matarese, 1997).

Doubly-labeled-water Technique

Plank and Graham (2003) reviewed the doubly-labeled-water technique which was another indirect calorimetry measurement methodology for measuring total energy expenditure of free-living individuals without the need for actual calorimeter. The metabolic data was collected over an average of 10 to 14 days and can be applicable in healthy population. The assumption of doubly- labeled–water technique included steady-state carbon dioxide and water turnover and constant body water pool size during measurement period. This is not realistic in the crucially ill population due to significant fluid shift in body water and changes of carbon dioxide production during first 1 to 2 weeks of admission into intensive care. Doubly-labeled-water technique provides only normal, daily and free-living energy expenditure information of an individual. The individual must consume oral dose of water containing a known stable isotopes of both hydrogen and oxygen (2H deuterium and 18O, an oxygen isotope) mix with the normal hydrogen and oxygen in the body water within a few hours. As energy is used, carbon dioxide and water are produced. Carbon dioxide is lost from the body in breath whereas the water is lost in breath, urine, sweat and other evaporations. As 18O is contained in both carbon dioxide and water, it is lost from the body more rapidly than 2H which is contained in water but not in carbon dioxide. The deviation between rate of loss of 18O and 2H reflects the rate at which carbon dioxide is produced which in turn can be used alone to estimate energy expenditure. Plank et al (2003) observed that the preexisting

conditions in doubly labeled water technique included steady-state carbon dioxide and water turnover and constant body water pool size during measurement period could be difficult to achieve in the critically ill population. It is common for the very ill to experience massive shifts in body water during the first or second week after admission. Advantages of doubly-labeled-water technique include appropriateness for all age groups as well as applicability in assessment of dietary intake and physical activity, energy requirement and effect of dietary and physical activity interventions. The disadvantages are 18O is quite expensive and skilled-technicians are required for analyzing the isotope concentration in body fluids. Doubly-labeled-water technique will not reflect information on snapshot of metabolic requirement in especially critically ill patients whose metabolism can vary with change of disease condition.

Mixed chamber technique

The mixed chamber technique is commonly used in commercial indirect calorimeters. The device can be used among spontaneous breathers through canopy, mouthpiece or mask as well as those relying on mechanical ventilation. Expired gas is collected and sent to the mixing chamber to streamline and even expired gas concentration. This type of calorimeter may have two analyzers that measure both continuous inspired and expired gas concentrations. Nonetheless, this calorimeter tends to be more expensive with complicated calibration procedure and can result in errors unless both analyzers are synchronized (Branson, 2004).

Breath-by-breath calorimeter

Holdy (2004) reviewed that breath-by-breath calorimeter did not have a mixing chamber and measurement was recorded by each breath from the individual. The site of gas sampling and volume measurement are being

taken at the proximal airways. Since there is no mixing chamber, the measurement is being averaged according to operator or manufacturer's preset preference. Gas collection is taken from mouthpiece, canopy or even handheld devices. Measured resting energy expenditure is actually calculated by assuming respiratory quotient at 0.7-1.0 using a modified Weir equation:

Energy expenditure in kilocalories = $3.94\ x\dot{V}_{O2} + 1.11\ x\dot{V}_{CO2}$ *x1440 minutes*

Closed-circuit calorimetry

Ainslie, Reilly, and Westerterp (2003) reviewed that closed-circuit calorimetry isolated individuals from the air on the outside. This method worked well for measuring resting or basal metabolic rate, however, the large volume of carbon dioxide produced during prolonged, strenuous exercise became problematic. Nevertheless, commercially available system using this technique was no longer manufactured (Branson and Johannigman, 2004).

Interpretation of Indirect Calorimetry

Energy Expenditure

Indirect calorimetry measurement can be both short term and continuous. The advantage of continuous measurement of total energy expenditure equals to 24 hours rather than a snapshot can reflect of metabolic pattern rather than a snapshot of expenditure. Measurement errors occur when ventilator is set at more than 60 percentage of inspired oxygen that leads to oxygen consumption increases markedly. Fortunately, indirect calorimetry technology has improved sensitivity to allow detection of 60-80% oxygen being inspired. Other factors that may lead to inaccurate measurement includes change in metabolic acid-based status, treatment

modalities such as extra-corporeal carbon dioxide removal and supplemental oxygenation therapy will disrupt gas exchange because of unpredictable oxygen consumption or carbon dioxide production (Plank et al, 2003). As a result, the calculation of substrate utilization and hence, energy expenditure will not truly reflect the actual situation.

Gas Exchange Measurement

Mechanical ventilation provides support for patients through the application of positive end expiratory pressure (PEEP). PEEP generates airway pressure that is greater than atmospheric pressure at the end of each exhalation (Dirckx, 1997). The level of PEEP is usually presented by cmH_2O and values set between 5 to 15 cmH_2O. Use of PEEP can sometimes be problematic because high pressure support from ventilators can alter gas partial pressures. Inaccurate pressure compensation can cause large measurement errors, particularly when inspired fraction of oxygen (FIO_2) is high. Error in measuring gas exchange can increase disproportionately when FIO_2 is greater than 0.6 and there is no automated device that will measure reliably at FIO_2 of more than 0.8. Most commercially available gas exchange measuring devices recognize the potential flaw and thus, include rejection algorithms (Walsh, 2003).

Leakage from the patient-ventilator circuit can also create error in indirect calorimetry measurement. The exact nature of error due to connection leakage often depends on the site it occurs and the design of the device. The common leaks are around tracheal tubes, humidifiers, and chest drains and further aggravates by high PEEP. Any suction performs on patients to remove excess secretions in their endotracheal or trachosotomy tube will simulate action of leak and invalidates the gas exchange measurement.

Indications To Perform Indirect Calorimetry Measurement

The application of indirect calorimetry measurement among critically ill population is highly recommended. The lack of accurate predictive equations to estimate patients' metabolic requirement makes it difficult for clinicians to prescribed nutrition support. The loss of and change in body mass (metabolically active tissues) because of immobility and duration of illness can vary metabolic requirement. On the contrary, change in the ratio of lean or metabolically active muscle mass could be irrelevant to patients' metabolic requirement (Porter, 1996). . Holdy (2004) stated that estimating metabolically active weight or feeding weight using predicted equations posed significant challenge in designing nutrition support regimens. Feeding weight is especially unpredictable in cachectic and obese patients. Holdy (2004) reviewed that indirect calorimetry could be most applicable among patients on mechanical ventilation and body mass index of less than 18 or more than 30. Other scenarios such as substantial tissue edema, limb amputation, failure to respond to conventional nutrition support, organ dysfunction, and change or wean from mechanical ventilation can also impact on energy expenditure.

Furthermore, energy expenditure of patients in the intensive care can vary with levels of clinical conditions and consciousness, fever and sedation as well as fever and operation. Under the circumstances, estimated requirements can easily be misinterpreted (Fontainea and Mullerb, 2011). da Rocha et al (2006) also pointed out that patients were indicated for indirect calorimetry measurement when there were clinical conditions that impact significantly on their energy expenditure, such as infection and inflammation, failure to respond to presumed adequate nutrition support as indicated by gain in body mass and improvement in nutrient-related biochemical indicators, patients who require individualizing and

fine-tuning of existing nutrition regimens.

Clinical Practice Guideline Steering Committee (2004) strongly recommended indirect calorimetry measurement among patients with conditions that are known to nutritional alterations such as neurologic trauma, paralysis, chronic obstructive pulmonary disease, acute pancreatitis, cancer with residual tumor burden, multiple trauma, amputations, without accurate body height and weight, failure to respond to regimen designed from estimated equations, long-term acute care such as chronic dependency on mechanical ventilation, severe sepsis, extreme body types and severe hyper- or hypometabolism. Indirect calorimetry provides measured metabolic data for difficult patient groups with complex disease conditions. .

Operating Conditions for Indirect Calorimetry Measurement

Steady State

Length of test period is vital to ensure possible extrapolation of single calorimetry reading to be representation of 24-hour energy expenditure. Therefore, steady state is introduced before obtaining indirect calorimetry data to improve accuracy and representation of measured energy expenditure especially for short duration (20 to 60 minutes). A short 15-minute protocol of calorimetry measurement could be as comparable to a 24-hour measurement in providing information on resting energy expenditure within an acceptable 4% error when steady state is achieved (da Rocha, 2006). The key was compliance to a well-defined steady state prior to measurement. Fung (2000) defined steady state as less than 10% fluctuation of oxygen consumption and carbon dioxide production. Thirty minutes of measurement duration after steady-state was achieved could be reflective of 24-hour energy expenditure. Author stressed that there could

be as much as 30% daily fluctuation in energy expenditure among the critically ill population, hence, steady state and repeated measurements especially on those with prolong stay could minimize measurement errors..

McClave et al (2003) defined steady state as change in oxygen consumption and carbon dioxide production of less than 10% over a period of 5 consecutive minutes. For those who cannot achieve the defined steady state, duration of indirect calorimetry test must be adequate to achieve coefficient of variation (CV) for oxygen consumption at less than or equal to 9.0 over the first 30 minutes. Nonetheless, for patients who failed to achieve steady state and were metabolically unstable, a minimum of 60 minutes indirect to 24-hour indirect calorimetry monitoring should be considered. McClave et al (2003) reviewed that steady state condition prior to indirect calorimetry measurement could promote validity and reduce errors influenced by artifacts. The application of steady state could minimize variation of resting energy expenditure measurement among patients on continuous or consecutive intermittent measurements. This variability could cause significant error in especially short-term measurement equal or less than 60 minutes and would be difficult to extrapolate the measurement into representation of 24-hour result. Steady state that was achieved by patients prior to the calorimetry test could improve accuracy of measurement and be reflective of 24-hour total energy expenditure.

Duration of Rest

Swinamer et al (1987) concluded that rest period of greater than 30 minutes were not necessary. Further research would deem useful to confirm and determine minimum duration to return to resting condition in critically ill patients with consideration of their sedation level. Most of the critically

ill patients were in supine position and resting in bed with minimal mobilization. Nonetheless, daily care activities, painful procedures including dressing change, etc. can potentially impact on resting energy expenditure (da Rocha, 2006).

Duration of Measurement

Studies showed that after discarding the data for the first 5 minutes to exclude artifact during indirect calorimetry measurement, an additional 5 minutes of measurement with less than or equal to 5% coefficient of variation in oxygen consumption and carbon dioxide production was comparable if 25 additional minutes of measurement with less than or equal to 10% CV. In other words, the more steady patients were prior to measurement, the shorter duration of measurement would become possible. If steady state is not possible within 30 minutes, measurement duration can be extended to promote accuracy of measurement. Duration of extended measurement can be determined by the CV (Holdy, 2004).

Body Position

Brandi et al (1996) reviewed that energy expenditure could be significantly elevated when patients were in the supine position than in the 30-degree head of bed elevation after surgery. The change in energy expenditure with various body positions might be due to different pattern of breathing. Since patients in the intensive care unit are commonly positioned to promote clinical safety and optimize treatment, thus, patients in this study were all being measured in their usual positions with strict adherence to resting period and steady state criteria prior to measurement.

Diurnal Variation

There was no evidence to show that resting metabolic expenditure in

mechanically ventilated and critically ill patients differed when indirect calorimetry measurement was taken during anytime of the day (Frankenfield et al, 1994, van Lanschot et al, 1988 and Zijlstra et al, 2007).

Room Temperature and Instrument Condition

A thermoneutral environment can be defined as avoidance of cool temperatures and drafts. Room temperature and conditions are important to avoid incidents such as shivering due to cold. Shivering can be thermogenic and elevates energy expenditure. Thermogenic disturbance may be aggravated among burn patients due to extensive heat loss from wounds that affect thermoregulatory protective effect. Humidity and pressure are less of a concern in intensive care unit unless patients are under specific therapies. Furthermore, instrument problems such as air leaks in chest tubes or the collection system during measurement may result in incomplete or incorrect gas collection (Fung, 2000). There is no primary research indicating any effect of light and noise on respiratory exchange ratio of critically ill patients (Compher, 2006).

Thermogenic Effect of Food

Fung (2000) suggested that patients relying on intermittent or bolus feedings could generate transient thermogenic effect of food and impact on accuracy of indirect calorimetry measurement. Energy expenditure post-meal reaches its peak at approximately 1 hour and return to normal in approximately 4 hours. If condition allows, indirect calorimetry measurement should be performed after an 8-hour fast. If intravenous infusion or enteral nutrients are given continuously, thermic effect from nutrients will be stable throughout the day and withholding patients' nutrition support for indirect calorimetry measurement is not necessary (Fung, 2000).

Porter and Cohen (1996) reviewed metabolic effect from food on individual energy expenditure. They discovered a 5 to 10% increase in energy expenditure after a mixed (combination of fat, protein and carbohydrates) meal that usually returned to normal about 4 hours post-feeding. The additional energy expenditure was induced by stimulation of the autonomic nervous system to process nutrients from dietary source. The types, compositions of nutrient and quantity of feedings for any patient could impact on interpretation of thermogenic effect of food. Tube feeding compared to intravenous nutrition delivery had been reported to elevate energy expenditure slightly more. Nonetheless, effect was found to be insignificant when patients were fed continuously as well as close to their energy requirement.

Since most of the patients in intensive care setting will be placed under continuous tube feeding mode, it is necessary to understand whether thermogenic effect of food can impact on measured metabolic rate. Alves et al (2009), Cankayali et al (2004) and Frankenfield and Ashcraft (2012) showed that there was presence of thermic effect with artificial feeding but results were inconclusive. An independent study on variation in metabolic rates before and after feeding as well as different modes of artificial tube feeding should be warranted.

Other Considerations in Indirect Calorimetry Measurement

Adjustment Factors

Holdy (2004) mentioned that resting energy expenditure measured by indirect calorimeter should be further adjusted to be closer to total energy expenditure. Routine activities in hospital such as nursing care, physiotherapy, examination procedures, etc. could potentially impose

additional 10% of total energy expenditure as activity factor (da Rocha, 2006). Fung (2000) reviewed that routine intensive care interactions might elevate energy expenditure in critically ill patients. Restlessness or agitation because of conscious level and magnitude of pain can mount up to 10% additional energy expenditure but return to baseline within an hour.

A 5% energy factor has also been proposed to compensate thermogenic effect of food when patients are on bolus or intermittent feeding during measurement. Nonetheless, it is not common practice in intensive care to put very ill patients on bolus or intermittent feeding mode rather continuous pump feeding. If patients are on continuous feeding, energy from thermogenic effect of food will be included as part of the measured values.
In summary, if patients can achieve steady-state prior to indirect calorimetry measurement, measured energy expenditure can be representative to 24-hour. Real-time indirect calorimetry measurement makes it unnecessary to factor in any additional adjustment. The liberal use of activity or adjustment factor can result in over-estimation of energy expenditure. Repeat calorimetry measurement may be able to capture most recent metabolic changes.

Respiratory Energy Ratio (RER) and Respiratory Quotient (RQ)
The ratio between oxygen consumption and carbon dioxide production is called respiratory quotient. The ratio can represent cellular respiratory quotient when storage of oxygen and carbon dioxide are in steady state. This ratio is often referred to as respiratory exchange ratio (RER) as well and it represents quantity of carbon dioxide expired over oxygen consumed to perform substrate oxidation (Walsh, 2003). Respiratory exchange ratio is an indicator for fuel mixture or substrate namely carbohydrates, fat and protein metabolism. Respiratory exchange ratio of 1.00 represents

oxidation of entirely carbohydrates because the number of carbon dioxide molecules produced is equal to the number of oxygen molecules consumed. Mixed diet may have respiratory exchange ratio of 0.85, protein 0.82 and fat 0.7. Respiratory exchange ratio has been as a guide to manipulate substrate provision during nutrition support. Nevertheless, elevation of respiratory exchange ratio can also reflect reduction in respiratory tolerance and occurrence of mild respiratory compromise. Clinical application of respiratory exchange ratio remains limited to being a marker of test validity and respiratory tolerance rather than adjustment of nutrition support regimen (Frary and Johnson, 2000).

Kan et al (2003) studied 54 hemodynamically stable, mechanically ventilated, and critically ill patients. Subjects who were underfed were found to have mean respiratory quotient of 0.91 ±0.19. Subjects who were fed within 10% of target energy requirement had mean respiratory quotient of 0.97 ±0.12. The remaining subjects who were overfed resulted in mean respiratory quotient of 1.16 ±0.32. McClave et al (2003) had examined clinical application of respiratory quotient as an indicator for under- and overfeeding. A total of 263 mechanically ventilated, critically ill older adult patients in long-term acute care who were on continuous intravenous nutrition support, enteral nutrition or combination of both were recruited. Underfed subjects (calories provision less than 90% of measured energy expenditure) had respiratory quotient of both less than 0.85 and 0.85 to 1.0. A small portion of underfed subjects had a respiratory quotient of greater than one but was considered by authors as inaccurate data. In addition, subjects who were fed appropriately had respiratory quotients at 0.85 to 1.0. Remainder of the adequately fed group also possessed respiratory quotient of less than 0.85 and greater than 1.0. Majority of the overfed group (43%) showed respiratory quotient

ranged from 0.85 to 1.0. Authors also analyzed non-protein respiratory quotient (NPRQ) and demonstrated that NPRQ greater than 1.0 could identify overfed patients at an acceptable specificity of 85.1%, but an unacceptably low sensitivity of 38.5%. Using NPRQ less than 0.85 to identify patients being underfed had a specificity of 72.3%, but a low sensitivity of 55.8%. Therefore, authors concluded that using respiratory exchange ratio might not be ideal in detecting feeding level of critically ill patients.

Respiratory exchange ratio had also been used to detect error of indirect calorimetry measurement. Brandi et al (1999) examined a total of 20 critically ill post-surgical patients who were sedated. The patients had all achieved stable pulmonary and hemodynamic status but dependent on mechanical pressure-controlled ventilation. Authors manipulated the minute ventilation of the ventilator and found that respiratory exchange ratio was more than 1.0 when patients were hyperventilating and less than 0.73 during hypoventilation. The results indicated that respiratory exchange ratio could be manipulated by changing ventilator setting. In addition, respiratory quotient was also shown to be influenced by patients' disease condition. Zauner, Schuster et al (2001) studied energy expenditure and substrate metabolism of 25 critically ill patients during fasting and administration of standardized intravenous nutrition which contained admixture of calories equivalent to 125% of measured resting energy expenditure. Subjects who were fasted overnight had mean respiratory quotient of 0.83±0.05. Respiratory quotient for those who were septic and fasting was 0.77±0.05 compared to 0.75±0.05 in the non-septic group. Septic patients with nutrition support resulted in mean respiratory quotient of 0.86±0.05 and non-septic group with same nutrition support being 0.82±0.04. Septic condition among the very ill population

appeared to lower respiratory exchange ratio despite with and without nutrition support.

In summary, respiratory exchange rate in especially the very ill population cannot directly indicate substrate oxidation and can be manipulated with ventilatory setting and when patients are not in steady state. Change in this ratio can only mean that indirect calorimetry measurement may be influenced by factors that will impact on the gas exchange.

Advancement in Medicine

Advancement in medicine with changes and improvement in sedation practice and pain management can influence energy expenditure. Terao et al (2003) conducted an indirect calorimetry study to examine relationship between sedation, resting energy expenditure and oxygen consumption in postoperative patients. A total of 32 patients undergoing either esophagectomy or surgery of malignant tumors of head and neck, dependent on mechanical ventilation and sedation for more or equal to 2 days post-operation were recruited. Ramsay sedation scale, body temperature and dose of midazolam were analyzed with metabolic rate being obtained by indirect calorimetry. Midazolam was sedative for induction and maintenance of sedation intravenously. Authors discovered that oxygen consumption index and resting energy expenditure decreased significantly with progressive light, moderate and heavy sedation. In other words, the deeper patients were being sedated, the lower their oxygen consumption as well as resting energy expenditure. Nonetheless, Bruder et al (1998) obtained energy expenditure measurements on 24 patients who were divided into four groups based on levels of sedation and a control group without any sedation. The results indicated that energy expenditure was significantly higher in the control group (without sedation) than the

other 3 groups with different levels of sedation. The advancement in medication may change the energy expenditure of patients at different times and during course of disease management. Therefore, medication will have to be well-documented during preparation for patients undergoing indirect calorimetry.

Measured Energy Expenditure and Protocol-Driven Nutrition Support

Indirect calorimetry measurement can assist in developing both individual nutrition care and protocols or guidelines to promote nutrition support in the intensive care setting. Barr et al (2004) conducted a study on implementation of enteral nutrition support protocol in intensive care unit. One hundred critically ill adult patients were sequentially recruited after staying in intensive care unit for 48 hours as control and additional 100 were recruited into the intervention group in which an intensive care management protocol was implemented. Nutrition algorithm was designed by reviewing nutrition literature using keywords intensive care, critical care, nutrition, enteral nutrition, parenteral nutrition, nutritional support and early enteral nutrition. Information was obtained from randomized controlled trials, meta-analyses, review articles, and consensus statements. The hypothesis was the introduction of protocol that led to increase in number of patients who were fed enterally and to be able to initiate nutritional support within 48 hours after intensive care admission and more rapid advancement in feeding volume. The protocol also aimed at providing guidance for feeding tube placement, initiation and strategies to tackle complications that led to slow progression of meeting nutrition requirement of patients.

Kiss et al (2012) conducted a study on patients in the intensive care unit on clinical outcomes with and without the implementation of nutrition

algorithm. Results of this retrospective study indicated that the difference in mean energy provision was significant between with and without nutrition protocol (p=0.023). Furthermore, cumulative energy deficit decreased with increased length of stay in the intensive care (p=0.011). However, this could mean that the higher calorie level was given to patients with adequate duration so that they could reach nutrition target. In a study by Barr et al (2004), they showed that patients in the intervention group (with nutrition management protocol) had 56% lower risk of death compared to the control group (hazard ratio 0.44, p=0.007). Patients in the intervention group stayed on mechanical ventilation shorter than the control group (17.9 ±31.3 vs 11.2 ±19.5 days, p=0.03) after adjusting for age, gender, severity of illness, type of admission, baseline nutritional status, and type nutritional support. Even though patients in the intervention group did not result in shorter intensive care as well as hospital length of stay but there was 56% reduction in risk of death (hazard ratio 0.44, p=0.007) independent of severity of illness, malnutrition categorization, age, gender, or diagnosis upon admission. Limitations in the study by Barr et al (2004) included various mortality rates were considered among medical and surgical patients as well as shorter duration on mechanical ventilation among medical patients could be related to their likelihood in receiving enteral nutrition than surgical patients.

Energy Expenditure and Economic Impact on Healthcare

The inositol setup for indirect calorimetry measurement can be costly and thus, clinicians need to justify the economic return to perform this metabolic assessment. Villet et al (2005) studied 709 patients from multiple hospitals and found that mean daily healthcare cost for each patient was 61% higher among those who were malnourished compared to the well-nourished. Amaral, Matos and Tavares (2007) also confirmed

that the overall hospital costing in Europe for the nutritionally at-risk patients could double those that were comparatively less nutritionally at risk. Thibault and Pichard (2010) mentioned that the more severe protein and energy deficit was among patients, the higher the incident of muscle wasting. The drastic catabolic effect of illness could lead to increase incidents of infection and multi-organ failure, prolonged ventilation, length of stay and mortality. Consequently, these negative outcomes would lead to a climbing global healthcare costing. Authors stated that positive clinical outcomes were possible if energy debt could be controlled during the first week of admission into intensive care unit. In addition, Braunschweig et al (2000) compared 404 patients who were well-nourished to those who were malnourished at discharge and discovered that hospital costs were almost double for malnourished patients. Neumayer et al (2001) also discovered that patients who were receiving both timely and adequate nutrition support had significantly shorter hospital stays and subsequently, lower hospital charge. McClave et al (1998) predicted close to 1.3 million US dollars in savings in the United States Healthcare System with proper enteral nutrition support.

Measured Energy Expenditure and Clinical Outcomes

The CPG Steering Committee (2004) recommended using indirect calorimetry to aid patient nutritional assessment and management, assessment of weaning success and outcome and assessment of the contribution of ventilation to metabolism. Negative protein-energy balance is common in intensive care unit and often unable to be compensated for because of disease condition induced hypermetabolism and accumulative energy deficit from delayed or suboptimal nutrition support. Persistent inflammatory response, prolong catabolism, frequent interruption in artificial feeding and inaccurate estimation of energy

expenditure all contributed to poor clinical outcomes including morbidity and mortality. Hence, it is important to match metabolic requirement of very ill patients to their nutrition support regimen. Nonetheless, there is a lack of study directly associating application of indirect calorimetry on clinical endpoints among the very ill population. Some expressed that it was unnecessary to doubt the accuracy of measured energy expenditure which had been used as golden standard to develop predicted equations (Thibault and Pichard, 2010).

With the complex clinical situations and inadequate provision of nutrition support to patients, cumulative energy deficits will continue to worsen. McClave, Kleber, and Lowen (1999) stressed that prescription of nutrition support regimens should be as precise as use of antibiotics, anticoagulation therapy, inotropic support, and ventilator management. Villet et al (2005) showed that more than 10,000 kilocalorie deficit over 1 week during patient course of stay in the intensive care was proven to prolong duration of stay and relate to poor mortality rate. Loss of skeletal muscle as a result of caloric deficit could be up to approximately 67% of the total body protein loss. Villet et al (2005) stated that indirect calorimetry provided better parameters to determine caloric requirement and assisted in constructing cumulative energy balance so that appropriate nutrition support regimen was possible and to promote weaning from mechanical ventilation by provision of optimal nutrition support.

The application of studies in assessing metabolic demands of the very ill population was limited because of the heterogeneity of subject population. The results of selected studies could only apply in a narrowly defined population. The constant interruption of nutrition support delivery also makes it difficult to match energy provision and energy expenditure .

Heyland and Cahill (2011) audit prospectively the association between caloric consumption and mortality among the very ill patient population. Data was collected from 352 intensive care units from 33 countries with a total of 7,872 mechanically ventilated, critically ill patients who had been admitted to the intensive care unit for at least 96 hours. Focus of the study was relationship of caloric consumption and 60-day hospital mortality. After adjustment for those who went directly to oral intake, with at least 4 days in the intensive care unit before progression to oral intake and excluding days of observation after progression to oral intake, the result was a significant benefit to increase caloric intake (unadjusted OR 0.73; 95% confidence interval 0.63–0.85). Authors concluded that patients who received more than two-thirds of their caloric prescription during their intensive care length of stay had a higher survival rate than those receiving less than one-third of their prescription (odds ratio 0.67; 95% confidence interval 0.56–0.79; $p < .0001$). Heyland and Cahill (2011) however, explained that the association between the caloric provision and mortality was significantly influenced by different statistical methodologies. This was especially obvious when duration of exposure to nutrition and length of stay in the intensive care unit were taken into consideration. Heyland and Cahill (2011) stressed that selected studies even excluded calories received by oral feeding into data analysis and thus, the effect of actual calories being provided from various routes was masked.

In summary, metabolic assessment using direct and indirect calorimetry can be applied in different population and clinical settings, however, the high initial setup cost may hinder its development. The reliability and accuracy of indirect calorimetry measurement depends largely on adequate patient preparation and appropriate interpretation. The accuracy and reliability of real-time measurements from indirect calorimetry will decrease with time

and thus, repeated measurement is highly encouraged especially if patients' conditions have changed.

Chapter 5: Experimental Measurement

Research hypothesis

The hypothesis of this study was significant difference in the energy expenditure of patients in the intensive care unit with initial diagnosis of sepsis during and upon liberation of mechanical ventilation.

Aim

The aim of this study was to determine whether there was difference in energy expenditure and substrate utilization among critically ill patients with and without mechanical ventilation.

Subject Recruitment

Patients age 18 and above, admitted into the intensive care unit with initial diagnosis of septic shock and dependent on mechanical ventilation were recruited. Inclusion criteria were hemodynamically stable with normal blood pressure, heart rate at <120 beats per minute, no sign of low cardiac output indicated by metabolic acidosis, poor urine output or myocardial ischemia at the time of test. Patients with surgical or medical complications including significant post-operative bleeding and major pulmonary complications were excluded.

Age, gender, body height and weight, length of stay in intensive care, duration on mechanical ventilation, Acute Physiology and Chronic Health Evaluation II (APACHEII) score of patients were recorded. Body height was measured from crown to bottom of feet resting in supine position in bed by soft measuring tape. Body mass was obtained from either past record, information from the next of kin or by calculating ideal body weight if none of the above could be obtained. Length of stay, duration on ventilator and Acute Physiology and Chronic health evaluation II scores

were collected from electronic registry for intensive care.

APACHEII is a classification system and one of the common disease severity indicators used in intensive care unit. The score is usually calculated by physician within 24 hours of admission to intensive care unit. The tool consists of scoring from 0 to 71 based on several indicators. The higher the score, the more severe disease state is and thus, subsequent risk of mortality (Knaus et al., 1985). The APACHE II score in this cohort could be interpreted as at a 30-50% risk of mortality.

Infection control

Patients resided in isolation rooms due to unknown source of infection and under surveillance for airborne infection, possessed comfort care directives or deemed to be in grave prognosis by case medical officers were excluded. Patients in isolation were recruited once their isolation status was lifted.

Ethics Consideration

The ethics committee of the Kowloon East Cluster hospitals, Hospital Authority, Hong Kong SAR approved verbal informed consent from patients and/or their next of kin (approval reference: KC/KE-09-0107/ER-2). There was neither risk nor harm inflicted to patients in this non-invasive and non-interventional study. The patients were hemodynamically stable and there was neither pain nor discomfort during the test. The chief investigator performed and monitored the test on site the entire time. Medical officers and nurses were also available at all times for medical issues. No incident resulted from the test and patients' medical treatment or clinical conditions were not affected. Furthermore, patients could benefit from structured and appropriate nutrition support according to practice guidelines being further developed

from this study.

Indirect calorimetry is non-invasive and there is no contraindication when applying on the critically ill population (American Academy of Respiratory Clinician, Clinical Practice Guideline Steering Committee, 2004). The committee stressed that unless hypoxemia, bradycardia or other adverse effects took place in even short term disconnection of ventilatory support for connection of measurement lines to the machine.

Recruitment

Subjects were recruited during daily ward round by the investigators. Eligible patients were arranged to receive indirect calorimetry measurement for energy expenditure during (pre-MEE) and upon liberation (post-MEE) from mechanical ventilation. Liberation from mechanical ventilation was defined as patients being independent from mechanical ventilator for at least 12 hours after the initial measurement.

Patient condition

The patients were rested in supine position and thermoneutral environment for at least 30 minutes prior to indirect calorimetry measurement. All routine nursing care including bathing, turning, etc. and rehabilitative procedures such as physiotherapy were held for at least 90 minutes before the indirect calorimetry measurement.

Nutrition support

Nutrition support is the provision of formulated enteral or parenteral nutrients to appropriate patients for maintaining or restoring nutrition balance (Bloch and Mueller, 2000). Nonetheless, it has been generally referring to any additional nutrition being provided to patients on oral diet

or solely to provide support for non-oral feeding route. Nutrition support was being provided to the cohort in this study through either tube feedings or oral diets. Calories from tube feedings were delivered to the patients through either nasal gastric or nasal jejunum tube. The former was fed directly into the stomach and latter was located in the jejunum. Rate of feeding was controlled by electric feeding pumps that could dispense feeding continuously at a fixed rate. Actual calories provided to patients were prescribed by physicians and progression was based on patients' tolerance. All of the feeding regimens remained unchanged between pre- and post-indirect calorimetry measurement. Dietitians were not involved in manipulation of patients' nutrition support.

In regards to intermittent feeding or overfeeding, TEF could increase energy expenditure by as much as 10%. Therefore, tube feedings were withheld 4 hours prior to indirect calorimetry measurement in order to minimize influence from thermogenesis of food. Furthermore, patients on continuous intravenous nutrition support and dextrose infusion which provided more than 15 kcal per kg per day equivalent to 5 liters of 5% dextrose per day were excluded to prevent similar thermogenic effect from dextrose source (Savard, 2008).

Preparation

Indirection calorimetry measurement started after 90 minutes of any change of ventilator setting. Resting period of not less than 90 minutes was also necessary after the following procedures and investigations due to disruption of steady state and necessary to allow restoration of steady state (da Rocha, 2006). The specific procedures include hemodialysis due to excess accumulation of bicarbonate in blood. Furthermore, potentially distressing procedures such as change of dressing, wound treatment, etc.

and routine nursing care or physiotherapy activities

Figure 1 Indirect Calorimeter used in this study

CCM Express (MedGraphics, United States) in Figure 1 was used to perform indirect calorimetry in this study. The CCM Express includes a gas exchange analyzer module for measuring oxygen consumption and carbon dioxide production. Patients interface with the calorimeter through the DirectConnect$_{TM}$ flow sensor and umbilical connector that connected to the terminal for gas analysis and calculation of metabolic data. CCM Express directly records oxygen uptake and carbon dioxide production for quantifying substrate utilization and energy expenditure.

Breathing Devices

Matarese (1997) introduced indirect calorimetry measurement for both patients capable of spontaneous breathing and dependent on mechanical-ventilation. Spontaneous breathers can utilize mouthpiece and nose clip, a mask or canopy for gas collection during indirect calorimetry. The disadvantages of mouthpiece and nose clip were inadequate seal, collection of saliva, dry throat, jaw fatigue, and inability to rest. A complete seal was advised if patient chose canopy as measuring device. Canopy system encloses patient's head in a clear hood and a built-in pump pulls room air through the canopy at a continuous speed. Gases being collected are shunted to a mixing chamber.

Patients who require supplemental oxygen is not feasible at this point to obtain indirect calorimetry measurement due to limitations in hardware, software and technique. The DirectConnect$_{TM}$ flow sensor in indirect calorimeter cannot register gas exchange readings when there is exogenous oxygen supply that bypasses the sensor. The error occurred when the oxygen supply disrupts steady inspiratory gas through the non-rebreathing valve. Exhaled airflow in patients dependent on mechanically ventilation is also being directed through the DirectConnect$_{TM}$ and data is collected alongside steady oxygen supply from the ventilator. The flow connections and gas concentration to specific ventilator can vary but recent indirect calorimeters are designed to pick up these changes automatically. A sample line should be placed between the endotracheal tube and the "Y" connector of the circuit (Figure 2).

Figure 2 – Indirect calorimeter connects to patient on mechanical ventilator

Dead space being created during mechanical ventilation can be minimized with the one-way valve design on the inspiratory side of the "Y" connector of the circuit. If the ventilator provides a continuous flow oxygen flow from the ventilator, the isolation valve should be in place to isolate the exhaled gas from the continuous flow from the ventilator.

Calibration

A system calibration on CCM Express was performed according to American Thoracic Society recommendation using a 3-liter syringe and flow sensor must first be set to zero to ensure no flow is introduced. The 3-liter syringe is for performing a volume calibration by introducing a designated volume into the flow sensor several times at different flow rates in three separate trials. CCM Express utilized an external gas calibration device for calibration with 2 gases; reference gas (21% of gas volume as O_2 and N_2 same as atmospheric composition) and calibration gas (12% O_2, 5% CO_2, N_2 same as atmospheric composition).

Testing Mode

Patient circuitry was composed of DirectConnect$_{TM}$ flow sensor and umbilical connected to the terminal (Figure 3).

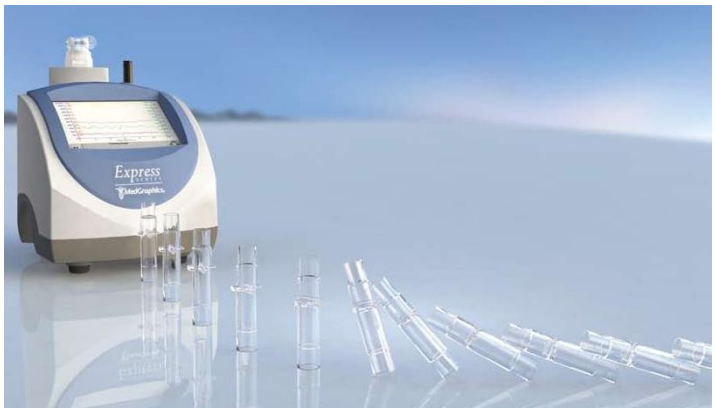

Figure 3 – Indirect calorimetry unit with the DirectConnectTM system.

For ventilator testing mode, CCM Express will auto-calibrate the continuous bias flow. Bias flow minimizes the work of breathing by allowing the patient to tap into a continuous gas flow rather than initiate flow through a delivery circuit. The system is able to differentiate between gas delivery to the patient's lungs and gas continuously flowing through the circuit (Medical Graphics Corporation, 2009). Measurements from indirect calorimetry are deemed valid once steady state is achieved by the patients. Steady state is defined as not more than 10% change in measured $\dot{V}_{O2}$ and $\dot{V}_{CO2}$ (McClave et al, 2003) in this study for 5 consecutive minutes. After patients were connected to the calorimeter, they were rested for an extra 5 minutes for acclimatization to the machine.

In this cohort, synchronized intermittent mandatory ventilation (SIMV) or continuous positive airway pressure (CPAP) was commonly used among the cohort for partial-controlled ventilatory support. The cohort received

indirect calorimetry measurement during SIMV or CPAP ventilator setting and upon liberation from mechanical ventilation.

Indications to liberate from mechanical ventilation is a combination of clinical judgment and objective criteria including satisfactory lung function with tidal volume of >5 mL/kg at a positive end-expiratory pressure level of 5 cm H_2O to ensure a PaO_2 of >80 mm Hg, $PaCO_2$ of <45 mmHg and fraction of inspired oxygen needed to be at 0.4 with spontaneous respiratory rate fewer than 30 breaths per minute. Patients' tolerance to lower ventilatory support with decrease in pressure support levels, muscle strength, spontaneous ventilation and level of consciousness were all being assessed again by attending physicians prior to actual discontinuation from mechanical ventilation (Serrano et al, 2005).

Ventilator-Dependent Patients With Tracheostomy

In this study, patients with tracheostomy were kept on stable ventilator setting for at least 12 hours before indirect calorimetry measurement. Patients were measured again when they were successfully liberated from mechanical ventilation for 12 hours. Indirect calorimetry measurements after liberation from mechanical ventilation were deemed valid when the patients continued without ventilatory support for the next consecutive 24 hours.

Ventilator-Dependent Patients With Endotracheal-Tube (ETT)

Besides tracheostomy, endotracheal-tube was also used to provide mechanical ventilation support for selected patients in this cohort. Endotracheal-tube is an external airway inserted into patients' lungs through the oral cavity. Under normal circumstances, the endotracheal-tube is used for short-term ventilatory support and will be removed completely from the patients upon liberation from mechanical

ventilation. This also means that the direct connection of the respiratory tubes from patients to the circuitry of the indirect calorimetry and mechanical ventilator will be lost. CCM Express is not capable of providing gas exchange in the absence of oxygen consumption information. Hence, indirect calorimetry measurement will not be possible if there is no complete circuitry connection to the DirectConnect$_{TM}$.

Automatic Tube Compensation Protocol

Automatic Tube Compensation (ATC) is a built-in function in majority of mechanical ventilators. One of the functions is to assist patients to overcome the resistance of the endotracheal tube in situ by delivering the amount of pressure necessary to overcome this tube resistance. Elsasser et al (2003) mentioned that Automatic Tube Compensation made was available in most ventilators for compensating decrease in flow-dependent pressure across an endotracheal tube during inspiration and expiration of a patent on mechanical ventilation. Automatic Tube Compensation allowed ongoing adjustment of pressure assistance during any ventilatory cycle according to the change in flow rate and flow-dependent pressure that decreased across the endotracheal tube. Pressure assistance from ventilators usually increases during inspiration and decreases with expiration. Automatic Tube Compensation mode exclusively relieve the pressure from existence of the endotracheal-tube and subsequent impact on work of breathing. Patients can experience reduction in work of breathing, preservation of spontaneous breathing pattern, synchronization with mechanical ventilation and improvement in respiratory comfort.

The ATC modified protocol allowed patients with endotracheal tube to retain the tube for connection to the indirect calorimeter while patients received no ventilatory support to simulate spontaneous breathing. This

makes it possible to recruit more than only patients on tracheostomy intubation. In order to minimize assistance from the ventilator, it was adjusted to only allow oxygen flow without positive end-expiratory pressure (PEEP) support and Automatic Tube Compensation mode was on the entire period of ventilatory support for patients in this cohort. PEEP is usually used to maintain and increase volume of gas left in the lungs at the end of exhalation. PEEP is designed to reduce shunting of blood through the lungs and improve gas exchange (Dirckx, 1997). Even though patients would be able to self-breathe while still retaining the endotracheal tube inside of them, the physical existence of the tube could impose discomfort and disrupt normal respiratory function. The reduction in respiratory work by using the automated tube compensation mode can promote successful weaning and making indirect calorimetry measurement possible (Cohen, Shapiro, Grozovski, Lev, Fisher, and Singer, 2006).

Modification In Calculating Resting Energy Expenditure and Substrate Oxidation

The indirect calorimeter automatically detected concentration of oxygen consumed and carbon dioxide produced by patients and data was converted into energy expenditure (kcal·d^{-1}) by a built in Weir's equation (da Rocha, 2006):

$$(3.914 \times VO_2 \cdot L \min^{-1}) + (1.106 \times VCO_2 \cdot L \cdot \min^{-1})(2.17 \times n \cdot gm \cdot \min^{-1}) \times 1400 \min \cdot day^{-1}$$

As mentioned by Porter (1996), the assumption of indirect calorimetry was complete oxidation of substrates (carbohydrates, protein and fat) and conversion into carbon dioxide, water, urea and energy. Energy synthesis through lipogenesis (production of fats) and ketogenesis (production of

ketones) are often overlooked. Lipogenesis (fat synthesis) usually takes place when patients are overfed. In addition, oxygen consumption and carbon dioxide production are assumed to be directly related meaning both of them must be totally involved in substrate utilization. Nevertheless, disruption in heart rate and adjustment of ventilator setting can alter minute ventilation and temporarily influence carbon dioxide production. These unexpected changes can promote large margin of errors when calculating resting energy expenditure using Weir's equation.

Jeukendrup and Wallis (2005) demonstrated various substrate oxidation models based on exercise intensity levels. Oxygen uptake during respiration and tissue levels are usually reflected truthfully in normal individuals. Carbon dioxide production in individuals will be steady with a stable bicarbonate pool. Authors observed that when glycolytic flux (glucose being broken down from glycogen) during high intensity exercise level coupled with lactate accumulation and clearance mismatch will hydrogen production increase. The body will then attempt to clear lactate accumulation (hydrogens) by means of increasing production and excretion of carbon dioxide.

Martinez et al (2003) and Weissman (1986) also explained that substrate oxidations during clinical crisis tended to developed heavy reliance on lipid than carbohydrate utilization. Nonetheless, Martinez et al (2003) focused on comparing substrate utilization between sick and healthy individuals whereas, Weissman (1986) used groups with different level of activities. Askanazi et al (1980) studied the effect of excessive exogenous calories and its impact on substrate utilization between stable and hypermetabolic patients. Calories were provided in the form of total parenteral nutrition, mainly intravenous infusion of nutrients. Patients were divided into

depleted (prior weight loss but medically stable) and hypermetabolic groups (septic or injured). There were a total of 18 patients in the depleted group and 14 in the hypermetabolic group and the patients were all receiving excessive calories mainly from glucose. The depleted group resulted in a 32% rise in carbon dioxide production compared to only 3% increase in oxygen consumption and respiratory quotient elevated from 0.83 to 1.05. The septic group on the other hand, had a significant increase of 29% ($p<0.001$) in oxygen consumption compared to 56% rise in carbon dioxide production. Mean respiratory quotient changed from 0.76 to 0.90 but never >1.0. Authors concluded that even with excess provision of calories in the hypermetabolic group, there was still net fat utilization illustrated by respiratory quotient consistently less than 1.0 and significant increase in oxygen consumption. The study demonstrated that calculated rates of glucose oxidation in the case of hypermetabolism among patients would not reflect true glucose oxidation rate by the rate that glucose was assumed to convert to fat.

Frayn (1983) stated that Weir's model had an inherent flaw to assume complete substrate oxidation. In other words, substrates that were consumed would match closely with their oxidation. During hypermetabolic state, substrate oxidation differs between sick and healthy individuals. Hypermetabolic patients relied heavily on gluconeogenesis (glucose produced from amino acids) for glucose production and oxidation. The excess glucose supply to these patients will convert into storage fats (lipogenesis) as well as those from endogenous lipolysis (fat mobilization from body storage). Frayn (1983) explained the importance of considering the influence of gluconeogenesis and lipogenesis in the very ill population so as to reflect actual substrate utilization in the body. He proposed that the calculated carbohydrate oxidation should be the sum of

rates of direct oxidation including source of glucose synthesized from gluconeogenesis that would be oxidized in the end. According to Frayn (1983), lipid oxidation should be the difference between rates of oxidation and synthesis from carbohydrates for instance, the net synthesis from excess exogenous glucose infusion in patients. Further interpretation on the calculation of substrate utilization would only be reasonable if a validation methodology such as isotopic study became possible.

True carbohydrate and lipid utilization according to Frayn (1983):

*Carbohydrate utilization (gm • min^{-1}) (If RER ≥0.7) =

($\dot{V}_{O2}$ - (2.03 × ***lipid oxidation))/0.746

****lipid oxidation (gm • min^{-1}) (If RER ≤1) =*

($\dot{V}_{O2}$ - $\dot{V}_{CO2}$)/(2.03-1.43)

Carbohydrate oxidation (grams • $minute^{-1}$) =

*Carbohydrate utilization - (**lipid synthesis × 1.923076923))

***lipid synthesis (If RER >1) =*

($\dot{V}_{O2}$ - $\dot{V}_{CO2}$)/(2.03-1.43) × -1

Measured Energy expenditure (kilocalorie per day) =

(*carbohydrate utilization ×3.74) + (***lipid oxidation x 9) × 1440

$\dot{V}_{O2}$ – Oxygen consumption $\dot{V}_{CO2}$ – carbon dioxide production

Urinary nitrogen was not collected in this cohort because of limitation in laboratory capacity. da Rocha (2006) stated that there was only 1% of error for every 12.3% of total calories metabolized from protein and thus, the equation could be simplified by excluding urinary nitrogen.

Statistical Analysis

Sample size was calculated by using a sample size calculator G*Power (Faul, Erdfelder, Lang and Buchner, 2007) based on significant value of <0.05 and power of 80%, the sample size should be 35. All statistical analysis was performed by EXCEL 2010 version 12.0 (Microsoft Inc.). Mean values and standard deviation were used to express descriptive statistics. Paired-t test was used to examine mean differences among measured energy expenditure during (pre-MEE), upon liberation from mechanical ventilation (post-MEE), actual energy consumption (KCAL), oxygen consumption ($\dot{V}_{O2}$), carbon dioxide production ($\dot{V}_{CO2}$) and substrate oxidation. Spearman test of correlation coefficient was used to assess relationship among variables. The results were reported with significance accepted at a level of $p<0.05$. Variability of data was expressed in standard deviation. Mean respiratory exchange rate ($\frac{\dot{V}_{CO2}}{\dot{V}_{O2}}$) was calculated by mean of individual oxygen consumption over carbon dioxide production.

Chapter 6: Results

Patients' Demographics and Clinical Descriptive Data

Thirty-five patients, 15 females and 20 males were included in the final results. Their baseline characteristics were shown in Table 1.

Table 1 – Descriptive statistics of patients' characteristics (N=35)

	Mena ±SD
Age (years)	69 ±10
Sex	Females 15 Males 20
Height (meter)	1.58 ±0.08
Body mass (kilograms)	59.01 ±7.63
APACHE Score (median)	22
Length of Stay (days)	45 ±65
Ventilation Days (days)	24 ±25

Mean duration of patients on mechanical ventilation (Ventilation Days) was 53% of their mean length of stay in intensive care (Length of Stay). Both standard deviations of length of stay in intensive care and duration on mechanical ventilation indicated a wide range of patients' bed and ventilator days in the intensive care. The median APACHE II Score was 22 and were translated to 30-50% mortality rate.

Table 2 – Patients' clinical diagnosis

● Central Nervous System (CNS) Infection	● Status epilepticus with sepsis
● Acute pancreatitis	● Type I respiratory failure and septic shock
● Herpes encephalitis	● Hospital-acquired pneumonia
● Pancreatitis and septic shock	● Urosepsis
● Perforated Peptic Ulcer	● Community-acquired pneumonia
● Parapharyngeal abscess and pneumonia	● Retropharyngeal abscess
● Liver abscess	● Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia
● Neck abscess, right pneumothorax	● Pancreatitis with retroperitoneal collection
● Sepsis	● Septic shock and acute renal failure
● Appendicitis and gangrene	● Cholangitis, septic shock and multi-organ failure (MOF)
● Ischemic gangrenous large bowel	● Brochopneumonia
● Acute cholecystitis with liver abscess and septic shock	● Necrotizing fasciitis, septic shock with amputation
● Severe Community-acquired pneumonia	● Necrotizing fasciitis
● Hip implant infection	● Severe pneumonia with respiratory failure
● Klesbsiella septicemia with meningitis	● Retropharyngeal abscess
● Acute cholecystitis with pneumonia	● Necrotizing fasciitis with septic shock
● Liver abscess	● Perforated peptic ulcer

There were originally 37 patients in the cohort. Two patients terminated their indirect calorimetry measurements prematurely because of sudden onset of post-operative seizure and known history of schizophrenia resulted in restlessness and irritation during measurement. Since these incidents could impact on stable energy expenditure measurement, they were excluded from the study and only 35 patients remained in the cohort.

Table 3 - Metabolic Information from Indirect Calorimetry Measurement

	Mean ±SD	P-value
PreMEE ($kcal \cdot day^{-1}$)	2090 ±489	<0.05
PostMEE ($kcal \cdot day^{-1}$)	1910 ±579	
Actual calorie consumption (kcal)	1148 ±495	
Actual calorie consumption and PreMEE		<0.05
Actual calorie consumption and PostMEE		<0.05
PreCHO Oxidation ($gm \cdot \min^{-1}$)	0.17 ±0.09	>0.05
PostCHO Oxidation ($gm \cdot \min^{-1}$)	0.14 ±0.08	
PreLipid Oxidation ($gm \cdot \min^{-1}$)	0.08 ±0.05	>0.05
PostLipid Oxidation ($gm \cdot \min^{-1}$)	0.09 ±0.07	
PreCHO Utilization ($gm \cdot \min^{-1}$)	0.19 ±0.1	<0.05
PostCHO Utilization ($gm \cdot \min^{-1}$)	0.15 ±0.09	
PreRER	0.87 ±0.14	>0.05
PostRER	0.84 ±0.12	
PreVO2 ($l \cdot \min^{-1}$)	0.31 ±0.08	0.05
PostVO2 ($l \cdot \min^{-1}$)	0.28 ±0.09	
PreVCO2 ($l \cdot \min^{-1}$)	0.26 ±0.06	<0.05
PostVCO2 ($l \cdot \min^{-1}$)	0.23 ±0.06	

PreMEE – energy expenditure during mechanical ventilation
PostMEE – energy expenditure upon liberation from mechanical ventilation
KCAL – actual calorie provision
PreRER – respiratory exchange ratio during mechanical ventilation
PostRER – respiratory exchange ratio upon liberation from mechanical ventilation
PreVO2 – oxygen consumption during mechanical ventilation

PostVO2	– oxygen consumption upon liberation from mechanical ventilation
PreVCO2	– carbon dioxide production during mechanical ventilation
PostVCO2	– carbon dioxide production upon liberation from mechanical ventilation
PreCHO oxidation	– carbohydrate utilization during mechanical ventilation
PostCHO oxidation	– carbohydrate utilization upon liberation from mechanical ventilation
PreLipid oxidation	– lipid oxidation during mechanical ventilation
PostLipid oxidation	– lipid oxidation upon liberation from mechanical ventilation

Table 3 showed the results in measured energy expenditure, actual calories consumption, oxygen consumption and carbon dioxide production during and upon liberation from mechanical ventilation among the cohort. These selected parameters were all statistically significant (Table 3). Thirty-three patients had received actual calories (KCAL) from tube feeding whereas, one patient did not receive any nutrition support and another one was on oral diet during entire study period.

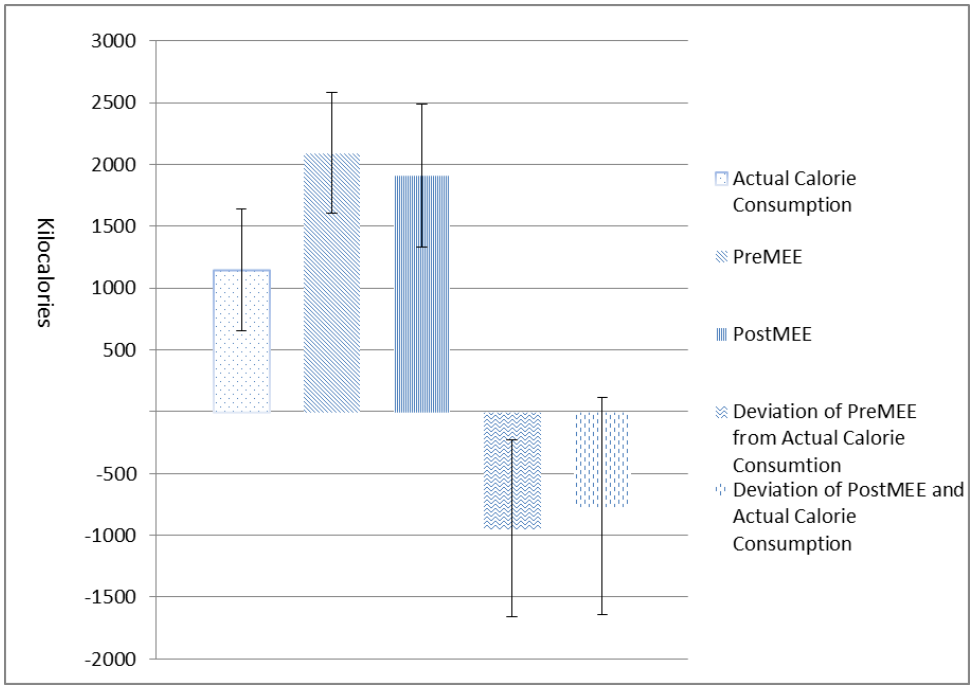

Figure 4 – Bar chart comparison with standard deviation of measured energy expenditure during (PreMEE) and upon liberation from ventilation (PostMEE) and actual calorie consumption (KCAL)

In Figure 4, measured energy expenditure during mechanical ventilation was 9% higher than upon liberation from it. The difference was statistically significant different (Table 3). The actual calorie consumption on the other hand, met only 55% of measured energy expenditure during ventilatory support and 59% upon liberation from ventilators. There was 1 patient with positive energy balance both with and without mechanical ventilation (1583 vs 1299 and 2378 vs 1502 kilocalories per day upon weaning with and without ventilators). Furthermore, 94% (n=33) of patients during mechanical ventilation and 77% (n=27) of them upon liberation from ventilator support received calories that were less than their measured energy expenditures.

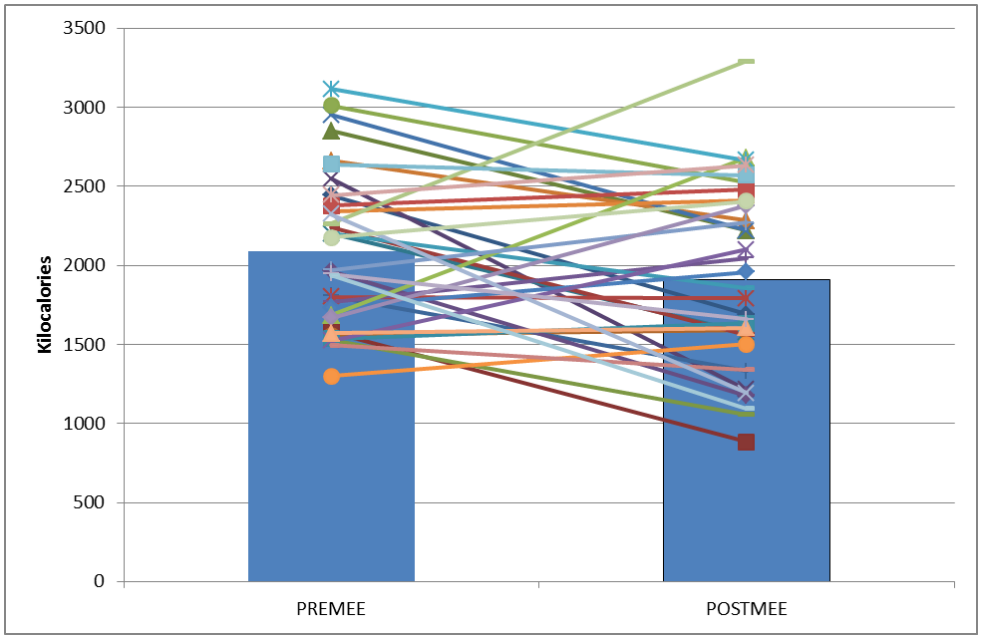

Figure 4a – Individual measured energy expenditure during (PREMEE) and upon liberation from mechanical ventilation (POSTMEE)

A total of 15 patients had measured energy expenditure lower during than upon liberation from mechanical ventilatory support (Figure 4a). The range of PREMEE was 1299 to 3115 kilocalories and POSTMEE was 882 to 3290 kilocalories.

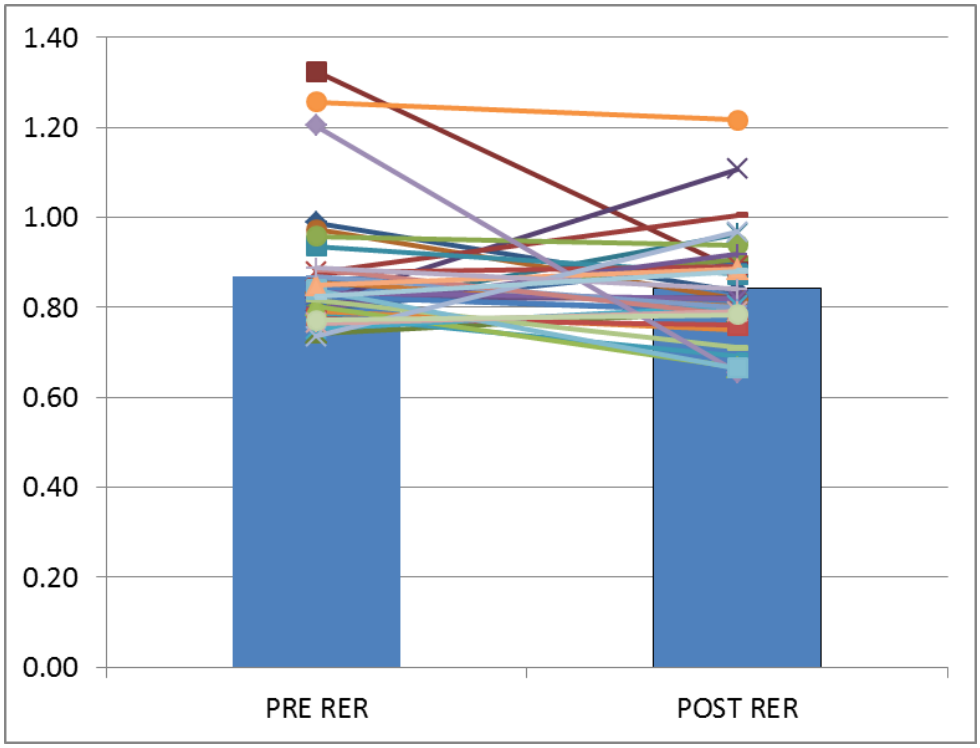

Figure 5 – Mean respiratory exchange ratio during (PRE RER) and upon (POST RER) liberation from mechanical ventilation

Mean respiratory exchange ratio (RER) in Figure 5 was higher in patients using mechanical ventilation than upon liberation from it but not statistically significant (Table 3). The mean respiratory exchange rates were the mean values of respiratory exchange ratio from individual patients. The range of respiratory exchange ratio during mechanical ventilation was 0.74 to 1.32 and without ventilatory support was 0.66 to 1.22. Respiratory quotient of more than 1.0 among patients with feeding that was less than their measured energy expenditure would be physiologically unreasonable (McClave et al, 2003).

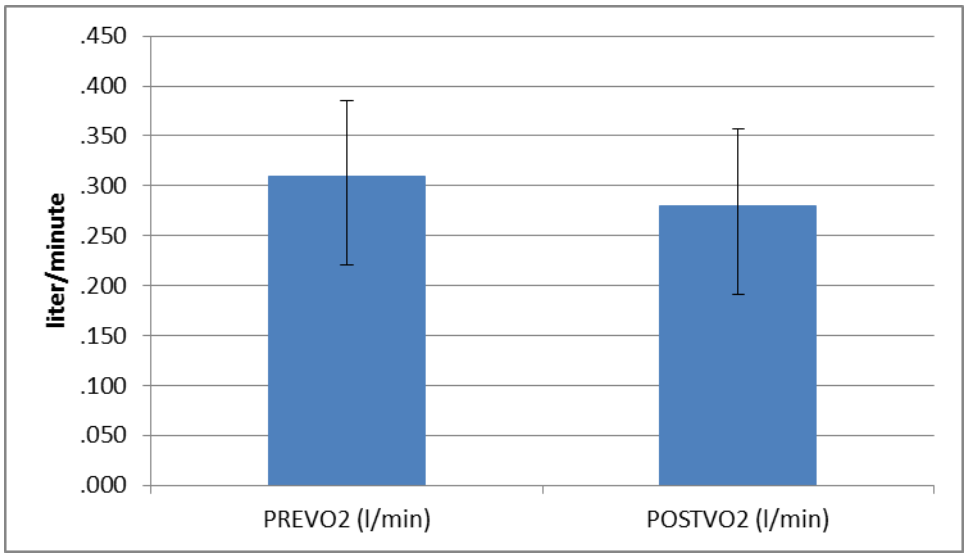

Figure 6a – Oxygen consumption during and upon liberation from mechanical ventilation
PREVO2 – oxygen consumption during mechanical ventilation
POSTVO2 – oxygen consumption upon liberation from mechanical ventilation

Oxygen consumption was 11% higher (Figure 6a) during than upon liberation from mechanical ventilation and they were significantly different as shown in Table 3.

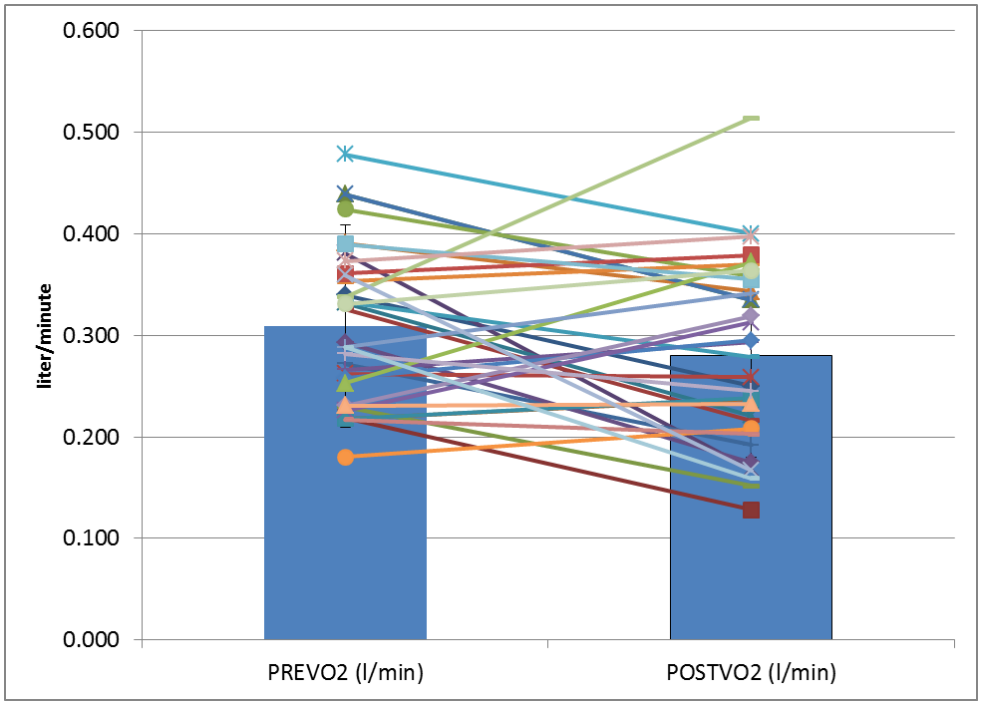

Figure 6b – Individual oxygen consumption during (PREVO2) and upon liberation (POSTVO2) from mechanical ventilation

During mechanical ventilation (Figure 6b), minimum oxygen consumption was 0.180 and maximum was 0.478 liter per minute, whereas, without ventilatory support, it ranged from 0.128 to 0.514 liter per minute.

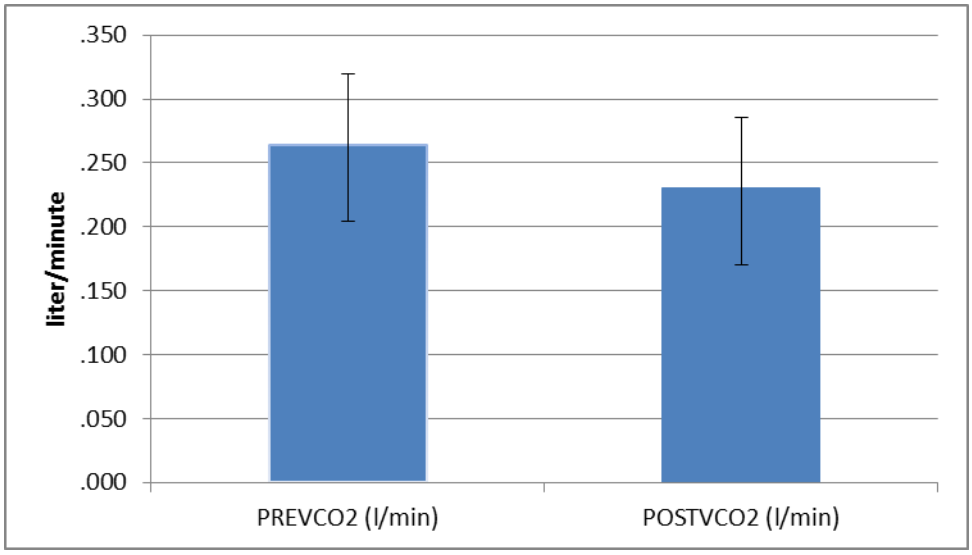

Figure 6c – Carbon dioxide production during (PREVCO2) and upon liberation (POSTVCO2) from mechanical ventilation

Mean carbon dioxide production (Figure 6c) was 13% higher during mechanical ventilation (PREVCO2) than without ventilatory support (POSTVCO2) and was statistically significant (Table 3).

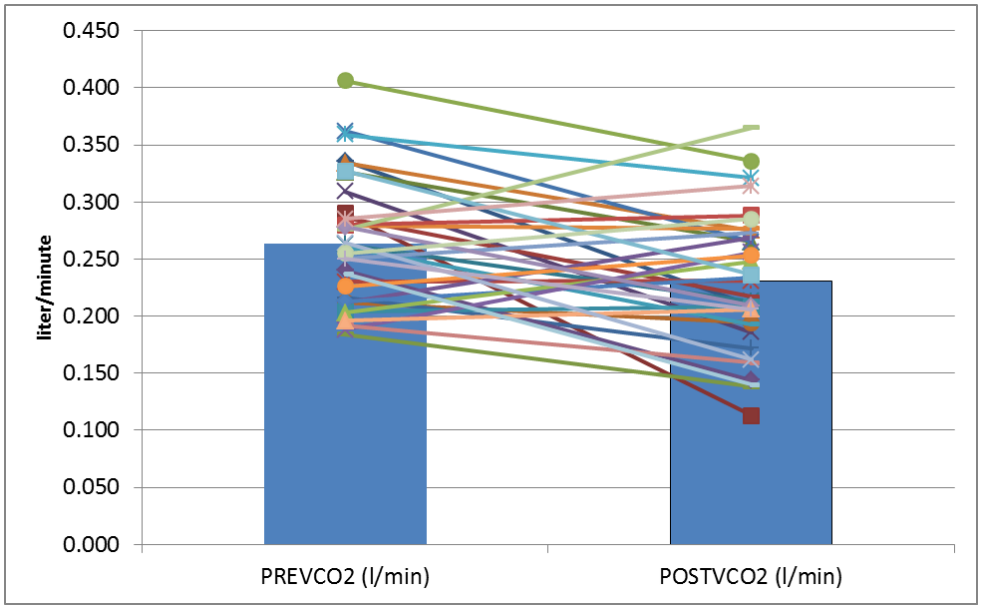

Figure 6d – Individual carbon dioxide production during (PREVCO2) and upon liberation from mechanical ventilation (POSTVCO2)

With mechanical ventilation, carbon dioxide production ranged from 0.184 to 0.406 liter per minute and upon liberation from mechanical ventilation, the range was 0.113 to 0.365 liter per minute (Figure 6d).

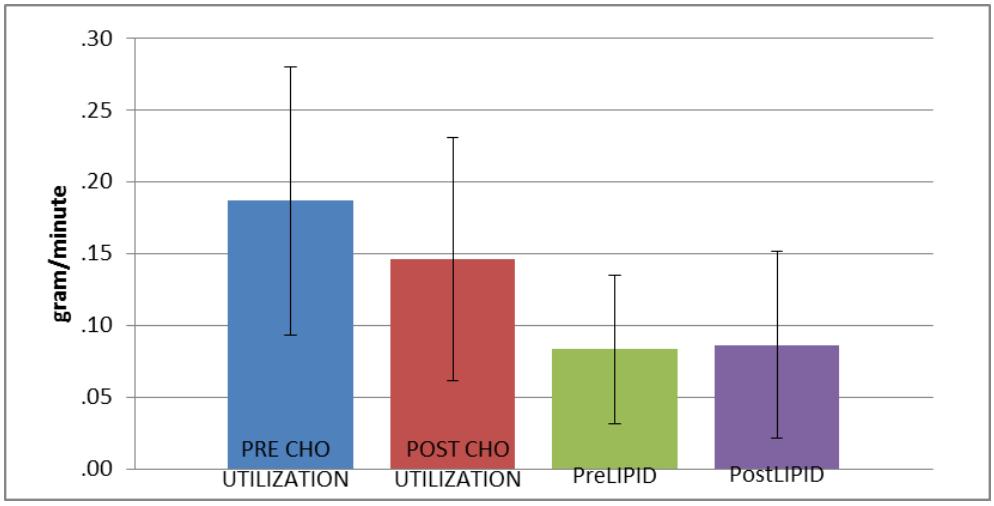

Figure 7 – Carbohydrate utilization (PRE CHO and POST CHO UTILIZATION) and lipid oxidation (PreLIPID and PostLIPID) during and upon liberation from mechanical ventilation.

Figure 7 showed that lipid oxidation was lower than carbohydrate utilization during and upon liberation from mechanical ventilation. Carbohydrate utilization during mechanical ventilation was 238% of lipid oxidation whereas it was 167% upon liberation from ventilatory support.

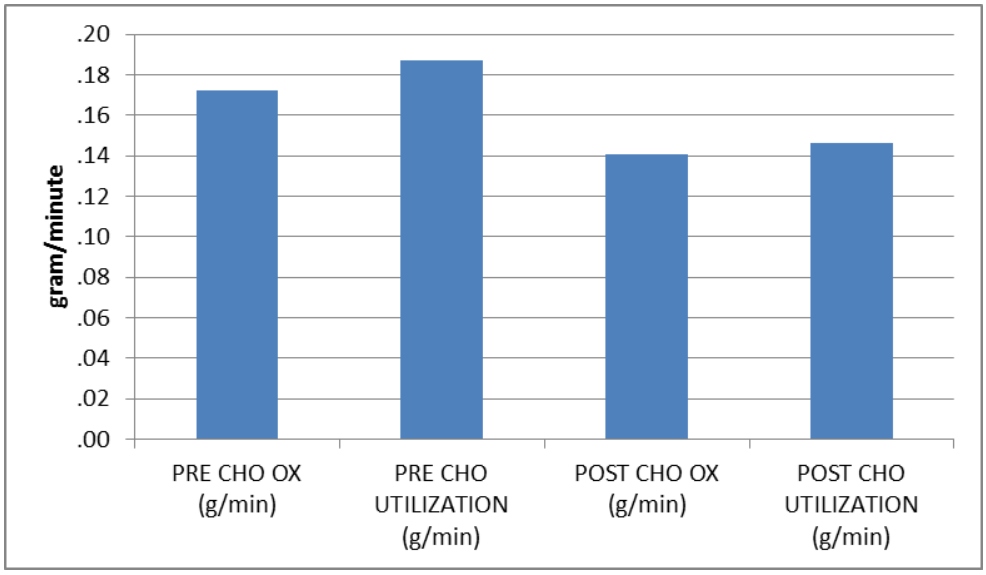

Figure 7a – Comparison of carbohydrate oxidation and utilization during (PreCHO) and upon liberation from mechanical ventilation (PostCHO)

Figure 7a showed that carbohydrate utilization rate was 12% higher than oxidation rate during mechanical ventilation and 7% upon liberation from ventilatory support. Carbohydrate oxidation was 21% and utilization was 27% higher with than without ventilatory support. Only carbohydrate utilization rate achieved statistically significant level (p=0.04) as shown in Table 3.

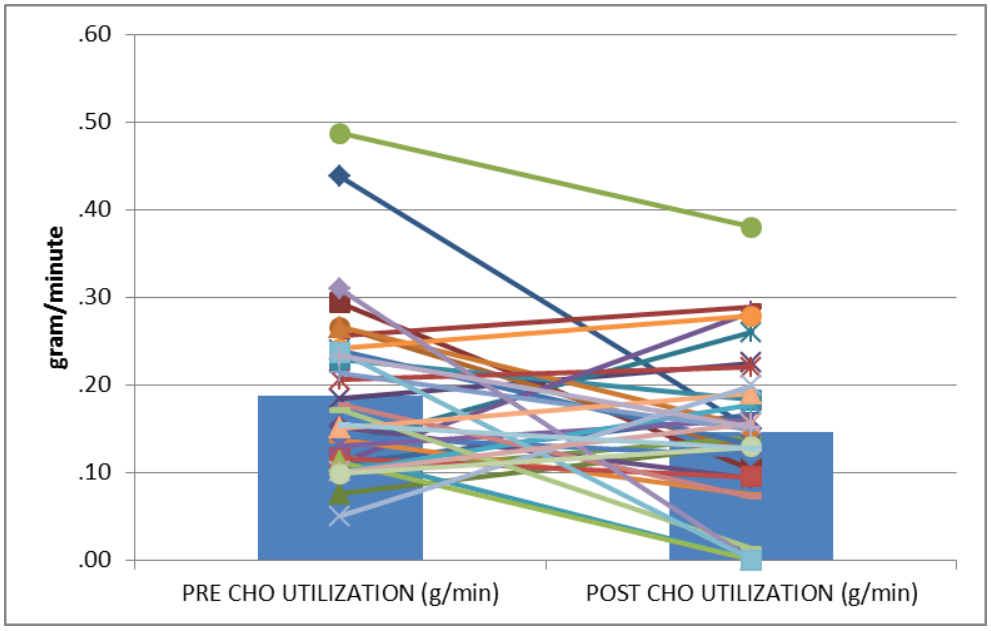

Figure 7b – Individual comparison of carbohydrate utilization during (PRE CHO UTILIZATION) and upon liberation from mechanical ventilation (POST CHO UTILIZATION)

Figure 7b showed that the minimum carbohydrate utilization was 0.05 and maximum was 0.49 gram per minute during mechanical ventilation and 0.00 to 0.38 gram per minute upon liberation from ventilation.

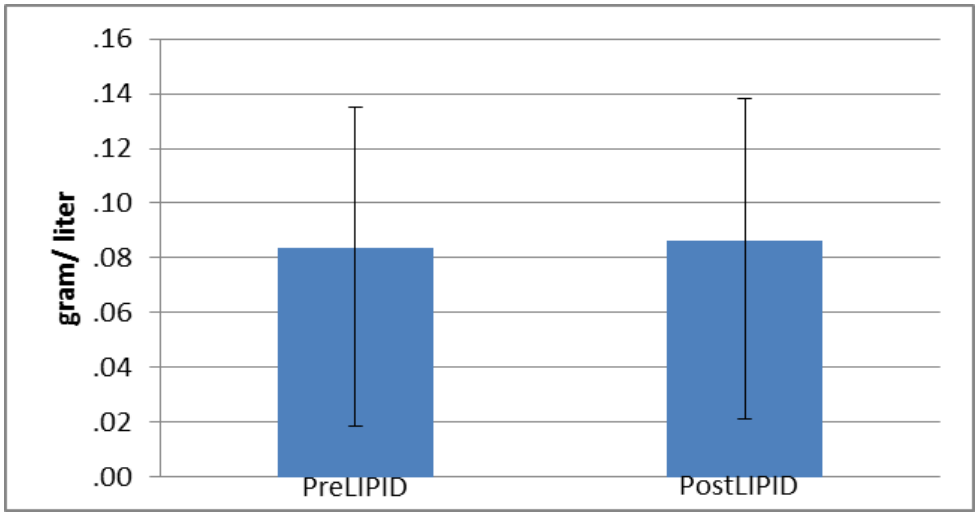

Figure 7c – Comparison of lipid oxidation During (PreLIPID) and upon liberation from mechanical ventilation (PostLIPID)

Lipid oxidation (Figure 7c) during mechanical ventilation was 89% compared to without ventilatory support but the difference was not significant (Table 3).

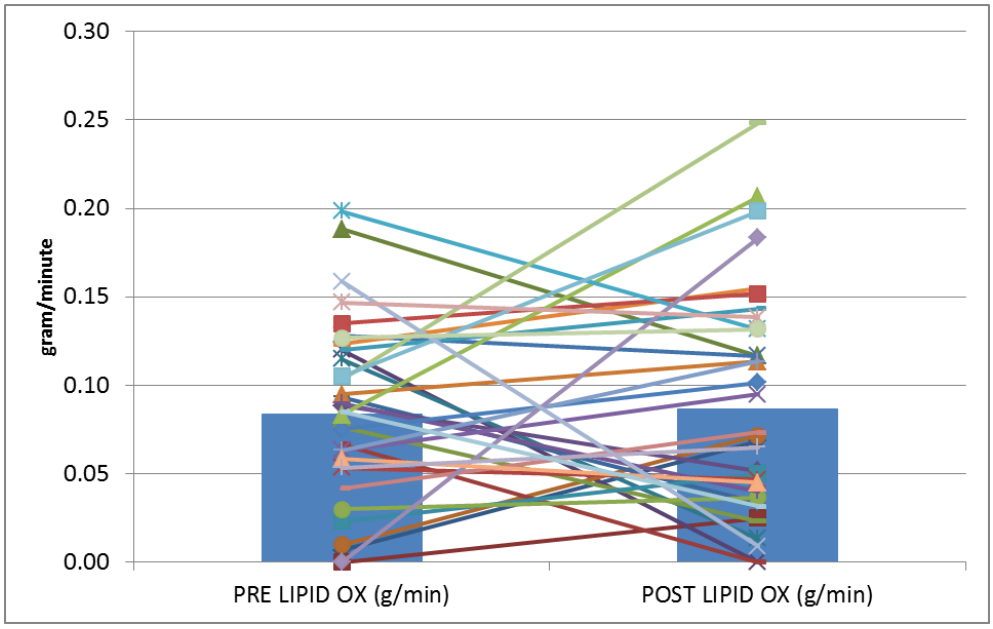

Figure 7d – Comparison of lipid oxidation during (PRE LIPID OX) and upon liberation from mechanical ventilation (POST LIPID OX)

Minimum lipid oxidation was 0.00 and maximum was 0.20 gram per minute during mechanical ventilation and ranged from 0.00 to 0.25 gram per minute upon liberation from ventilation (Figure 7d).

Table 4– Spearman correlation coefficient values during and upon liberation from mechanical ventilation

	Spearman *rho*	**p-value (<0.05)**
Pre and Post MEE	0.47	<0.05
PreMEE and KCAL	0.03	>0.05
PostMEE and KCAL	-0.21	>0.05
Pre and PostRER	0.24	>0.05
Pre and PostCHO	0.08	>0.05
Pre and PostLipid	0.32	>0.05
KCAL and vent days	0.55	<0.05
KCAL and LOS	0.41	<0.05
KCAL and PreVO2	-0.002	>0.05
KCAL and PreVCO2	0.19	>0.05
KCAL and PostVO2	-0.25	>0.05
KCAL and PostVCO2	-0.19	>0.05
PreCHO and PostCHO	0.08	>0.05
PreLipid and PostLipid	0.32	>0.05
Pre and PostVO2	0.49	<0.05
Pre and PostVCO2	0.40	<0.05
PreVO2 and PreCHO	0.14	>0.05
PostVO2 and PostCHO	-0.20	>0.05
PreVCO2 and PreCHO	0.23	>0.05
PostVCO2and PostCHO	0.08	>0.05
PreVO2and PreLipid	0.74	<0.05
PostVO2and PostLipid	0.82	<0.05
PreVCO2and PreLipid	0.37	<0.05
PostVCO2and PostLipid	0.91	<0.05

PreMEE – energy expenditure during mechanical ventilation
PostMEE – energy expenditure upon liberation from mechanical ventilation
KCAL – actual calorie provision
PreRER – respiratory exchange ratio during mechanical ventilation

PostRER	– respiratory exchange ratio upon liberation from mechanical ventilation
PreVO2	– oxygen consumption during mechanical ventilation
PostVO2	– oxygen consumption upon liberation from mechanical ventilation
PreVCO2	– carbon dioxide production during mechanical ventilation
PostVCO2	– carbon dioxide production upon liberation from mechanical ventilation
PreCHO	– carbohydrate utilization during mechanical ventilation
PostCHO	– carbohydrate utilization upon liberation from mechanical ventilation
PreLipid	– lipid oxidation during mechanical ventilation
PostLipid	– lipid oxidation upon liberation from mechanical ventilation
Vent days	– duration of mechanical ventilation
LOS	– length of stay in intensive care

Table 4 showed the correlation coefficients of measured energy expenditure, oxygen consumption, carbon dioxide production, substrate oxidation, actual calorie provision, duration of mechanical ventilation and length of stay in intensive care. There was a moderately strong, positive and significant inter-individual correlation in measured energy expenditure during and upon liberation from mechanical ventilation. The elevated measured energy expenditure during mechanical ventilation led to similar upward trend when patients were liberated from ventilators.

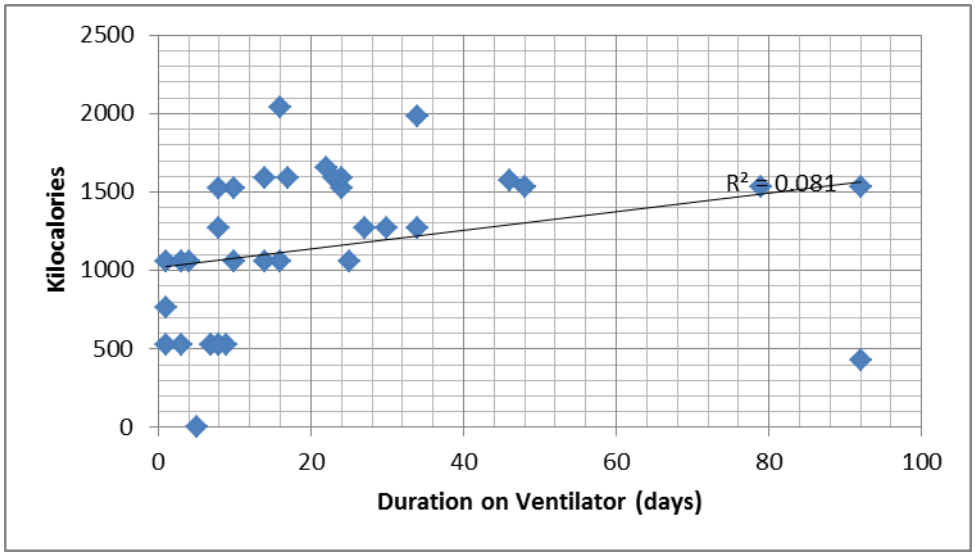

Figure 8 – Spearman Correlation Coefficient of actual calorie consumption (KCAL) and days on mechanical ventilation (vent days)

A significant and moderately strong positive relationship was observed (Figure 8) between actual calorie consumption and duration of patients on mechanical ventilation support. The longer patients stayed on the mechanical ventilation, the higher their calories consumption.

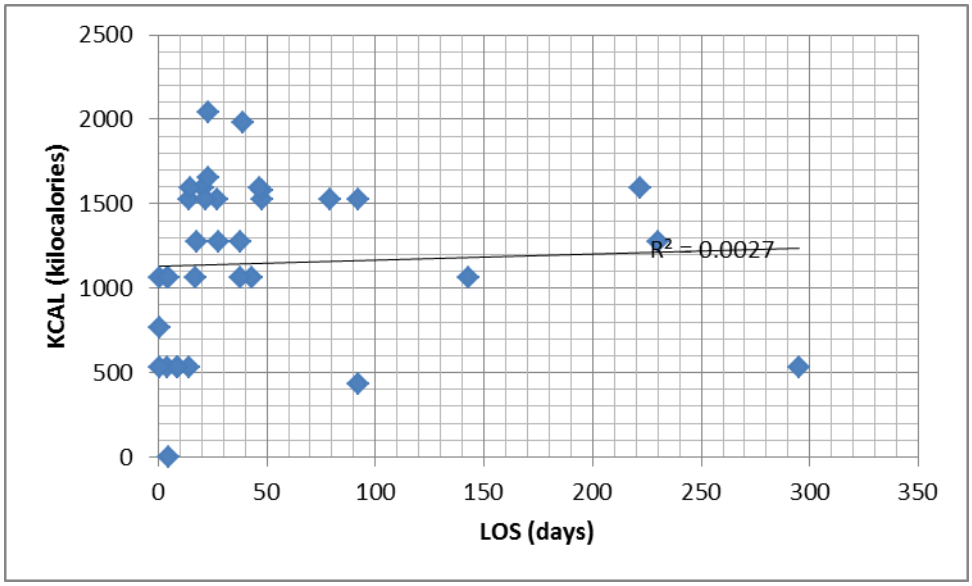

Figure 9 – Spearman correlation coefficient of actual calorie consumption (KCAL) and length of stay in intensive care (LOS)

Figure 9 showed similar result in which a positive and moderately strong correlation between length of stay and daily actual energy consumption. Patients who stayed longer in intensive care were related to higher caloric consumption.

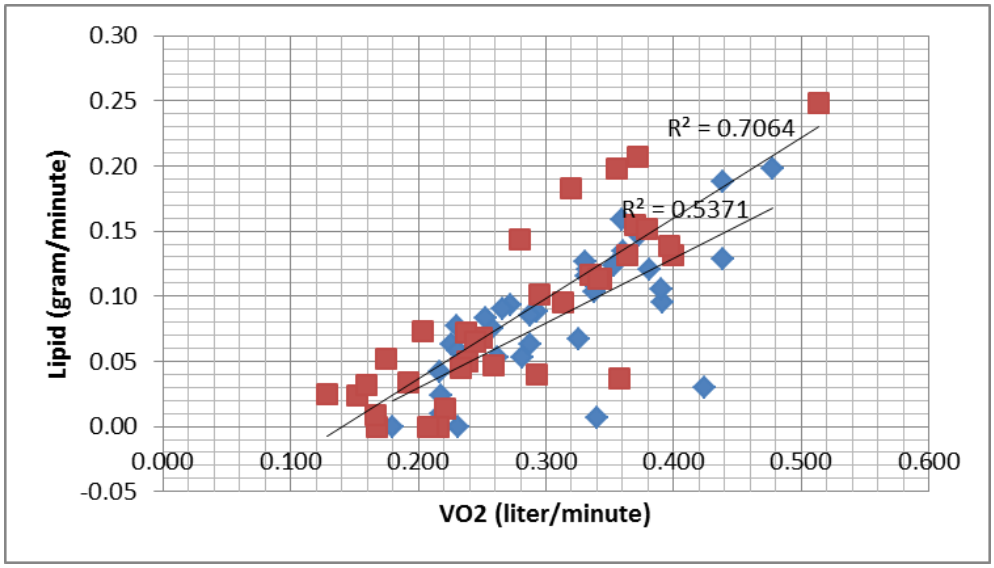

Figure 10 – Correlation of oxygen consumption (VO2) and lipid oxidation (Lipid) both during and upon liberation from mechanical ventilation

Oxygen consumption during and upon liberation from mechanical ventilation was both strongly and positively correlated with lipid oxidation. The correlation was also statistically significant (Figure 10).

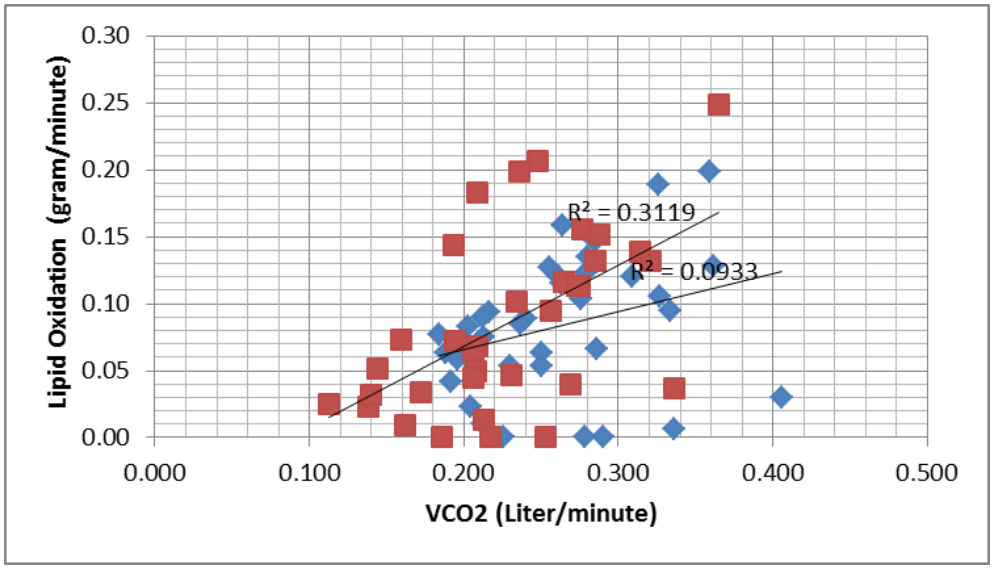

Figure 11 – Correlation of carbon dioxide production (VCO2) and lipid oxidation both during and upon liberation from mechanical ventilation

Patients also demonstrated a strong and positive correlation in lipid oxidation and carbon dioxide production upon liberation from mechanical ventilation in Figure 11. The correlation without ventilatory support was stronger than during mechanical ventilation (Table 4).

Chapter 7: Conclusion and Discussion

Measured energy Expenditure and Mechanical Ventilation Support

This is a pioneer study to investigate energy expenditure and substrate utilization among patients with initial diagnosis of septic shock during and upon liberation from mechanical ventilation. Using critically ill patients in clinical trials remain difficult and technical because of their heterogeneous nature. The heterogeneity refers to the different clinical conditions and related treatments including mechanical ventilation that can hinder development of quality clinical trials to obtain useful information on their metabolic status.

Recruitment criterions of critically ill patients in most studies are usually defined by location, intensive care in this case and seldom a specific disease. There are myriad of clinical conditions in intensive care and some of them can actually be physiological and biological abnormalities that lead to the formation of syndromes rather than well-defined diagnosis. Moreover, patients whose disease progression warrants admission to the intensive care can be in their late stages. The various severity of disease development will also produce different test results on the same individual. There are additional challenges in defining disease processes such as sepsis, septic shock, etc. Therefore, it is vital to comprehend pathophysiology development of the disease or syndrome and appreciate its prevalence. Furthermore, by understanding the risk factors of the selected conditions and limitations of the clinical syndrome, appropriate patient can be selected for specific trials (Herbert, Wells and Marshall, 2002).

Septic shock can be life-threatening and the subsequent septic condition can prolong metabolic alteration among patients in the intensive care. Critically ill patients in recovery phase continue to suffer from long term

condition called *chronically critically ill*. These are patients who survive from life-threatening illnesses but remain hospitalized for an extended period of time. They continue to show poor functional status and may develop into adult failure-to-thrive syndrome (Higgins et al, 2006). Rehabilitative processes such as sitting out and mobilization in ward demand additional energy. As previously mentioned, Dickerson et al (1991) and Kreymann (1993) demonstrated the impact of severity of sepsis (sepsis vs. septic shock) on energy expenditure. Energy expenditure continued to elevate in septic patients as they progressed from ebb to *flow phase* (Uehara, 1999). This cohort was recruited by a single diagnosis of septic shock but severity of their septic development was not part of the consideration in this study. Therefore, the inter-subject variation in energy expenditure during and upon liberation from mechanical ventilation can result from different levels of septic condition.

Baseline characteristics in this cohort were comparable and patients were all clinically stable upon indirect calorimetry measurement. Sedation prescription was protocol-driven and levels of sedation thus, prescriptions were similarly among the cohort and throughout the study. Critically ill patients sometimes require different level of sedation or paralytic agents to minimize discomfort due to existence of artificial airway (intubation for ventilatory support) and physical pain. The impact of sedation was mentioned previously on lower oxygen consumption and resting energy expenditure index ($kcal \cdot day^{-1} \cdot m^{-2}$) (Terao et al, 2003). Nevertheless, the lower level of sedation upon weaning from mechanical ventilation in this study did not result in higher energy expenditure than during ventilatory support.

In regards to impact of metabolically active muscle mass on energy

expenditure, actual body mass of the cohort could not be obtained in the intensive care because of patients' critical conditions as well as the availability of appropriate measuring devices such as built-in bed scale. Fluctuation in body weight because of addition and removal of resuscitation fluid also made it difficult to truly reflect patients' actual body mass. There was potential loss of muscle mass, development of *chronic critically ill syndrome* and prolong total bed rest among the cohort and could contribute to lower measured energy expenditure upon weaning from mechanical ventilation.

Work of breathing is energy-demanding for the critically ill population because of ventilation and respiratory perfusion mismatch. This mismatch led to inadequate gas exchange and subsequent hyperventilation to try and achieve homeostasis (Benotti and Bistrian 1989). Although positive pressure support from mechanical ventilation provides assistance to patients for maintaining acceptable respiration, active engagement of the lungs by the ventilator can also be energy-costing. The contraction of diaphragm triggers by mechanical ventilation becomes an interaction of patient and the ventilator and is called "entrainment". Entrainment is often unrecognized in the critically ill patients who are dependent on mechanical ventilation. Akoumianaki et al (2013) studied entrainment in a group of sedated patients on mechanical ventilation. The positive pressure support from ventilator mentioned previously was a one-way mechanism initiated from the ventilator and entrainment illustrated a different neuromechanical coupling. The most significant part of entrainment is the inspiratory effort of patient that occurs and repeats over a specific phase of the ventilator cycle. Authors categorized entrainment to be 1 neuromechanical respiratory cycle is linked to 1 ventilator cycle for 5 consecutive cycles. Patients contribute to the neuromechanical respiratory

cycle to couple with 1 ventilatory machine cycle even in sedation. This dynamic interaction between patients and the mechanical ventilators may further increase energy expenditure. In addition, the repeated trials of "rest" and "work" cycles upon weaning from mechanical ventilation can further elevate energy expenditure (Taggert et al, 2000).

Measured Energy Expenditure and Nutrition Support

This cohort exhibited significant negative energy balance between caloric consumption and measured energy expenditure both during and upon liberation from mechanical ventilation. Patients did not receive any dietetic consultation during the entire period of the study. Underfeeding is common in intensive care because of conservative approach in providing nutrition support for the very ill patients as well as the frequent interruption by complications, procedures and examinations. The lack of continuity in nutrition support delivery for the cohort could hinder progression to meet their nutrition targets (Kan et al, 2003 and Reid, 2006). The actual calories provided to patients in fact remained the same before and after mechanical ventilatory support despite their change in energy demand. The negative energy balance in this cohort was the simultaneous impact from underfeeding and elevated energy expenditure.

A structured nutrition support protocol or algorithm can provide guidance for clinicians to prescribe nutrition support appropriately. The protocol can also heighten clinicians' awareness to minimize negative energy balance and reduce potential cumulative energy deficit when patients' length of stay in hospitals was prolonged (Kiss et al, 2012). Adequate nutrition support and improvement in patients' clinical outcomes was well documented (Heyland and Cahill, 2011 and Neumayer et al, 2001). Malnutrition results in loss of muscle mass and can be the key to maintain

normal breathing (Askanazi et al, 1982).

Correlation of Actual Calorie Provision and Days on Ventilation

In this cohort, positive relationships were identified between duration of mechanical ventilation and length of stay in the intensive care and actual caloric consumption. In other words, the longer the cohort stayed in the intensive care, the more caloric intake they acquired. Length of stay in intensive care was longer than duration on mechanical ventilation because patients would usually be weaned from mechanical ventilation prior to transfer to general card wards (Table 1).

Respiratory Exchange Ratio and Substrate Oxidation During and Upon Liberation from Mechanical Ventilation

Mean respiratory exchange ratio in this study was calculated by individual mean of respiratory exchange ratio. Respiratory exchange ratio was observed to be influenced by factors not directly related to substrate oxidation. Majority of patients received nutritional calories that were less than their measured energy expenditure and had respiratory exchange rate of <1.0. Those who had achieved positive energy balance showed respiratory exchange ratio of >1.0. Exception of one patient with respiratory exchange ratio at 1.0 during mechanical ventilation but was in negative energy balance. All of the patients in this study had stabilized from the initial septic shock and achieved acid-base balance. Therefore, the subsequent action of respiratory compensation (increase carbon dioxide production) due to lactic acid accumulation should not be a reason for the patient who was underfed but had respiratory exchange ratio of ≥1.0. As explained by Martinez et al (2003), change in clinical conditions, liver abscess in that particular patient and different modes of ventilatory support could influence oxygen consumption and carbon dioxide production and

produced misleading substrate oxidation calculation.

Carbohydrate oxidation and utilization were higher than lipid oxidation both with and without mechanical ventilation similar to previous study (Martinez et al, 2003). The patients in this study with respiratory exchange rate of >1.0 and possessed positive balance between caloric consumption and measured energy expenditure was in net lipid synthesis because of overfeeding that led to subsequent conversion of excess carbohydrates into fats (lipogenesis). There were patients who had respiratory exchange ratio of >1.0 but in negative energy balance would likely be a result of artifact during measurement (McClave, 2003). Carbohydrates continued to be the major metabolic substrate being utilized among patients with and without mechanical ventilatory support in the intensive care.

The assumption of complete substrate oxidation in the indirect calorimetry measurement will not truly reflect substrate utilization among critically ill patients because of dominating lipolytic, lipogenic and gluconeogenic activities. Substrate oxidation measured from indirect calorimetry is based on matching oxygen consumption and carbon dioxide production at the respiration and tissue level. Glucose that is synthesized from non-glucose source will still oxidize for energy production. Lipid mobilization was observed to continue even when glucose-based calories were provided in the very ill population (Jeevanandam, Young, and Schiller, 1990). Furthermore, lipolytic and lipogenic processes demanded energy (Wolfe, 1997) and was shown to possess positive correlation between lipid utilization and carbon dioxide production in this cohort. Frayn's model helps to incorporate substrate utilization from different domineering metabolic pathways during critically ill condition that contribute to energy

production.

Oxygen Consumption and Carbon Dioxide Production and Mechanical Ventilation

Positive pressure support from mechanical ventilators and unknown duration of sepsis development can contribute to increase in oxygen demand and carbon dioxide production observed during mechanical ventilation in this cohort. The increase in respiratory muscular activity experienced by the critically ill population is a response to restore balance of their respiratory function (Askanazi et al, 1982). The lower oxygen consumption upon liberation from mechanical ventilation can be a result of discontinuation of steady oxygen supply when ventilatory support is removed. Patients in this cohort were also recovering from their physical ailment and gradually resuming normal respiratory function. As mentioned previously by Bellani et al (2010), oxygen consumption tended to be higher among patients with difficulty weaning from mechanical ventilation. Furthermore, any fluctuation in fraction of inspired oxygen between the 30-second measurement intervals by the indirect calorimeter, measured oxygen consumption can over- or underestimate actual oxygen consumption (Branson and Johannigman, 2004). Unfortunately, this study did not identify the potential deviation between measurement intervals.

Application of Indirect Calorimetry in the Critically Ill Patients

It is challenging to perform indirect calorimetry in the critically ill population. The constant change of clinical conditions makes it difficult to maintain periods of stable oxygen consumption and carbon dioxide production (steady state) to ensure accurate indirect calorimetry measurement. Gas exchange fluctuates unpredictably during course of

stay in the intensive care (McClave, 2003). Patients should be allowed to acclimatize to the indirect calorimeter, usually a minimum of 5 to 10 minutes before measurement was performed (McClave, 2003). Those who exhibit fluctuation in gas exchange pattern should be measured beyond 30 minutes (Holdy, 2004 and McClave, 2003). Multidisciplinary coordination is also pivotal for patient preparation so that they can be fasted and rested adequately before indirect calorimetry measurement. Indirect calorimetry offers an opportunity to measure real-time energy expenditure to facilitate nutritional assessment. Clinicians should increase reliance on indirect calorimetry measurement over predictive equations for assessing patients' nutritional requirement. The application of specific predicted equations is narrow because of limitation by different variables that can be incorporated (McClave et al, 1999). Application of indirect calorimetry measurement can also promote awareness of cumulative caloric deficit in the critically ill population. Repeated indirect calorimetry measurements are ideal for fine-tuning nutritional therapy.

Development of New Testing Protocol for Patients Using Endotracheal Tube

In order to recruit more potential patients and accommodate those who used endotracheal tubes for mechanical ventilation, an *Automatic Tube Compensation* protocol upon weaning from ventilator was developed. The different extubation methodology for patients on endotracheal tubes can be problematic to obtain circuitry connection for the indirect calorimeter. Tolerance to the *Automatic Tube Compensation Protocol* in this cohort was based on subjective observation of patients' tolerance such as signs of restlessness, irritation, or respiratory distress. The *Automatic Tube Compensation Protocol* is novel and very useful for indirect calorimetry measurement among patients on endotracheal tube intubation.

Way Forward

This study sheds light into the various aspects of metabolic profile among critically ill patients with and without mechanical ventilation. The asynchronization between patients' respiration and ventilatory cycles, positive pressure support from mechanical ventilation and repeated "rest" and "work" cycle during weaning from ventilatory support potentially impact on energy demand of critically ill patients. A different substrate oxidation calculation model was applied to incorporate the alteration from different metabolic pathways in the very ill population. The development of *Automatic Tube Compensation protocol* allows patients using endotracheal tubes to be measured upon weaning from ventilator.

Besides to obtain larger sample size to strengthen power of future studies, there should be further investigation into factors that impact on energy expenditure and will change with disease progression. The inter-subject variances including loss of muscle mass, severity of disease conditions, respiratory response to work of mechanical ventilation (entrainment), and different modes of ventilation (assisted versus total controlled) and their relation to metabolic profile of patients should be further explained. The economic benefits of accurate metabolic information among the critically ill population can bring positive impact on healthcare savings (Braunschweig, 2000 and Neumayer et al, 2001) and should also be focus of future studies.

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